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CARBON MONOXIDE

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ABSTRACT

Data available on the health effects associated with exposure to carbon monoxide were reviewed in March 1980 in order to make recommendations concerning the Ambient Air Quality Objectives for carbon monoxide (CO) which have been prescribed pursuant to subsection 4(2) of the Clean Air Act. The respective maximum desirable and maximum acceptable carbon monoxide concentrations specified by the Ambient Air Quality Objectives are as follows:

8-hour time - weighted averages of 6 and 13 mg/m^3 (0.5, 1.3 Pa) and;
1-hour time - weighted averages of 15 and 35 mg/m^3 (1.3, 3.0 Pa).

The critical health effect of exposure to carbon monoxide observed in the general population is a deterioration of vigilance. Under conditions of fatigue, boredom, and limited arousal, effects are seen at a blood carboxyhaemoglobin (COHb) content of from 3 to 4%. There is limited evidence linking deterioration of certain vehicle driving skills to loss of vigilance, but there has been no convincing demonstration that the frequency of traffic accidents is increased at this level of poisoning.

Groups where an unusual sensitivity to CO may be anticipated include those exposed to hypoxia (clinically or by reason of altitude sojourn), those with an increased respiratory minute volume, and those with an increased endogenous production of carbon monoxide. Very few studies concerning CO exposure in patients with cerebrovascular disease have been conducted. Individuals who are most vulnerable to carbon monoxide exposure seem to be patients with coronary vascular and/or peripheral vascular disease. In both these categories, the time to exercise-induced pain is hastened at a blood COHb content of 2.5 to 3.0%. Cardiac death rates also may be increased at a blood COHb content of greater than 3.5%.

High altitude exposure interacts with CO poisoning. At moderate altitudes, an ascent of 300 metres may be equated to a 1% increase of blood COHb content. Thus, individuals living above 1000 metres are particularly vulnerable to small doses of CO, and specific air quality recommendations are needed for such populations.

It is concluded that the model of Coburn et al., (1965) provides the best available indication of relationships between ambient CO exposure and blood COHb levels, and that there should be a two-fold safety margin separating the maximum permissible limit of CO exposure and detectable responses to CO. It is further recommended that monitoring data be averaged over periods of 1, 8 and 24 hours, with reporting of both the median and the number of observations exceeding the permitted limit, air quality criteria being based on the "second highest" value. Only maximum permissible partial pressures should be specified for sea-level locations, appropriate values being 1.5 Pa for 1-hour, 0.9 Pa for 8 hours, and 0.8 Pa for 24 hours.

OVERVIEW AND RECOMMENDATIONS

Existing Regulations

Canadian interest in air pollutants dates back to 1930, when the first ambient air quality criteria and standards were proposed following investigations on the health effects of several industrial pollutants (Katz and Drowley, 1966). Under the provisions of the Clean Air Act, the federal government recommends air quality criteria for the protection of public health and welfare (Lucas, 1972), but with a few specific exceptions, the responsibility for regulation and enforcement is exercised by the provinces and municipalities (Katz and Drowley, 1966). For example, in Ontario the "Air Pollution Control Act" of 1958 gives the provincial Minister of the Environment power to (i) investigate air pollution problems; (ii) recommend methods of monitoring, and (iii) assist municipalities in the drafting of air pollution control bylaws (Ontario Gazette, 1974). While municipalities regulate emissions from most types of fuel-burning equipment and incinerators, industrial emissions fall under direct provincial jurisdiction.

While this sharing of authority may be an unavoidable consequence of our current Canadian constitution, it has several undesirable practical consequences:

(i) standards of air quality recommended by the federal government are not necessarily accepted by all provinces. There is thus a potential for honest confusion concerning legal requirements, and industries with high emission rates may play one province against another.

(ii) pollution does not respect political boundaries, so that a province or municipality may be faced with the difficult task of attempting to control contamination originating within another jurisdiction, and

(iii) discussion is inevitably focussed upon local problems, to the possible neglect of global consequences of ever-increasing air contamination.

Current federal recommendations (Ouellet, 1978) specifiy three control levels - the maximum desirable level, the maximum acceptable level, and the maximum tolerable level (Environment Canada, 1973). The maximum desirable level is equivalent to the World Health Organization (WHO) Level I (WHO, 1964), where pollution can be detected, but there are no physiological changes or other adverse effects upon human health. The maximum acceptable level is a level of pollution where full compensation is possible (Hatch, 1962). The maximum tolerable level represents the limit of physiological compensation (Hatch, 1962). Adverse effects include a deterioration of visibility, damage to vegetation, and impairment of sensory function (Goldsmith, 1962), and discomfort may be sufficient to cause an individual to change his place of residence.

Applying these principles to carbon monoxide, the federal government currently recommends time-weighted average concentrations of CO as follows:

Average period	Maximum desirable		Maximum acceptable		Maximum tolerable	
	ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3
1-hour	13	15	30	35	-	-
8 hours	5	6	13	15	17	20

In Ontario, required levels correspond to the maximum acceptable objectives (30 ppm for 1-hour, 13 ppm for 8 hours and 8 ppm for 24 hours). The U.S. limits have a differing statistical basis (second-highest reading of year), with a ceiling of 35 ppm for 1-hour and 9 ppm for 8 hours. Requirements of other jurisdictions are summarized in Table 1.

Critical Health Effect(s) for the General Population

The critical factor which should serve as the basis for limiting exposure of the general population to CO seems to be a deterioration of central nervous function. This is a consequence of impaired oxygen delivery to the brain rather than a local poisoning of intracellular enzyme systems. Exercise performance is also measurably impaired at about the same level of CO exposure.

Detection of a threshold for effects upon the central nervous system is hampered by the limitations of current test procedures, which have a wide variability in scores and prolonged learning curves. Furthermore, the brain has a substantial reserve capacity that can be called upon in emergencies (such as the impairment of local oxygen delivery). If the subject is aroused (anxious concerning the experiment, taxed by the test procedure, or animated by friends), the reserve capacity is utilized, but if he suffers from boredom and sensory isolation (CO exposure in a small booth), the reserve is not invoked and sensitivity to CO is increased.

Under resting conditions, some compensation for CO poisoning is possible through an increase of cerebral blood flow. Few changes of psychomotor performance are thus to be anticipated until the potential for cerebrovascular adjustment has been overloaded. In practice, CO exposure may give rise to transient effects (for example, Beard and Grandstaff, 1972; Fodor and Winneke, 1972), raising the possibility that it takes a certain dose of CO or a certain time to induce compensatory mechanisms.

Table 1 - Summary of authors reporting changes in vigilance and other central nervous functions, with corresponding COHb readings

Function	Blood COHb%	Author	Comments
Vigilance task	1.8	Beard and Grandstaff (1972)	?Exaggerated by sensory isolation. Effect reversed at highest dose
Errors of time estimation	1.8	"	"
Vigilance task	2.3-3.1	Fodor and Winneke (1972)	Effect disappeared with continuation of experiment
Vigilance task (weaker tones)	? 3.0	Groll-Knapp et al., (1972)	COHb not measured
Auditory duration discrimination	2.5-4.0	Beard and Wertheim (1967)	?Sensory isolation COHb not measured
Visual intensity discrimination	3.0	Beard and Grandstaff (1970a)	?Sensory isolation
Tracking task	3.0	Mikulka et al., (1971)	Authors suggested statistically unrealiable
Choice reaction time	3.5-4.0	Ramsey (1972)	Many negative results for simple reaction time
Visual acuity	4.5	McFarland et al., (1974)	
Vigilance (Brighter pulse)	5.0	Horvath et al., (1971)	
Mental performance, finger dexterity	7.2	Bender et al., (1971)	

The earliest detectable effect of CO upon the central nervous system seems to be a deterioration of vigilance (failure to detect a difference in light brightness, tone loudness, or signal length), with parallel problems of time estimation (Table 1). This conclusion is consistent with the very extensive wartime studies of altitude-induced hypoxia. The precise COHb level in blood at which an effect can be detected remains unclear; various reports indicate saturations ranging from 1.8 to 7.6%. In a number of studies where a high threshold has been described, the reason for this has been a failure to test responses to smaller doses of CO or the use of an insufficent sample of subjects relative to the variability of the test methodology. On the other hand, the findings of Beard and his colleagues are widely regarded as anomalous, since in their experiments the arousal of subjects was artificially reduced by confining them to a small audiometric booth throughout a lengthy CO exposure. Furthermore, Beard and his associates did

not measure blood COHb, but were content to estimate this from inhaled CO or alveolar pressures. The importance of arousal is plain in tests of vigilance. Nevertheless, a boring task carried out in an audiometric booth bears some similarity to the demands of solo highway driving, a situation where significant CO exposure is particularly likely to occur. The deterioration of central nervous function should probably be regarded as falling within the bounds of physiological compensation (i.e., maximum acceptable concentration). In at least two of the experiments cited (Table 1) the disturbance was indeed corrected as the dose of CO was increased (although the mechanism of compensation, whether it was use of cerebral reserve, increase of arousal, or augmented cerebral blood flow remains to be determined). We may conclude that the probability of detecting impaired vigilance depends greatly upon test circumstances, but that healthy young adults commonly show some response at a blood COHb content of 3 to 4%.

Although the immediately measured changes are physiological in nature, more serious health consequences could arise from a deterioration of vehicle-driving skills. Unfortunately, available evidence on this point remains equivocal. The techniques of operating a laboratory driving simulator differ substantially from the skills needed in normal operation of a car. Tests on simulators have been severely criticized from several points of view, and available data at best reaches the borderline of statistical significance following exposure to larger doses of CO than those needed to reduce vigilance. Thus Wright et al., (1973) described a deterioration of careful driving habits ($0.1 > P > 0.05$ by X^2 test) with a 3.4% increase of COHb (total COHb of nonsmokers > 5%). Experiments conducted while driving actual vehicles have noted a similar pattern of disturbance, but only after exposure to quite large doses of CO. For example, Weir et al., (1972) reported perceptual narrowing (7% COHb) and decreased use of the rear-view mirror (12% COHb). One factor minimizing the effects of CO during normal driving is that the cerebral reserve is not fully committed, so that some compensation for loss of function is possible. The decreased margin of cerebral reserve would not normally be detected, but nevertheless could be critical in responding to an emergency situation. McFarland (1973) demonstrated one facet of this diminished reserve in that subjects demanded more roadway viewing time after CO exposure.

There is as yet no convincing research linking CO exposure with the frequency of vehicle accidents. Although Yabroff et al., (1974) found that an increased proportion of accident victims had blood COHb levels greater than 5%, this association could have arisen from (i) a linkage between smoking and alcoholism, (ii) accidents caused by the mechanics of smoking, (iii) accidents due to other constituents of cigarette smoke, and (iv) accidents related to the personality of cigarette smokers. Nevertheless, there are few negative reports and the issue remains important; there is thus scope for a large study that relates blood COHb content and traffic accidents after making independent allowance for smoking habits and alcohol consumption.

Deterioration of effort tolerance has been demonstrated statistically at blood COHb levels of 4% and above. The loss of aerobic power is roughly proportional to COHb formation, and increases linearly with COHb at saturations above 6%. The existence of a threshold for the decrease of maximum oxygen intake is controversial, but may be suspected by analogy from the effects of altitude hypoxia upon physical performance. Experiments on athletes have shown little impairment of oxygen transport or endurance effort at altitudes of less than 2000 metres. On the other hand, most studies of CO exposure and exercise tolerance have been based upon small samples of young if not athletic subjects. It has not yet been demonstrated convincingly that there is a significant zero intercept of the COHb/performance line (as would be observed with a threshold), and it remains possible that a statistically significant deterioration of performance might be demonstrated at a COHb level of less than 4%, given a sufficient sample size. The currently accepted threshold of 4% reinforces the air quality criterion set by observations on vigilance. Again, the response is a physiological rather than a pathological disturbance, and it can thus be considered as defining a maximum acceptable range of pollution. The loss of oxygen transport has practical consequences for an endurance athlete or a man performing a long shift of heavy physical work, but in the ordinary sedentary person there is merely a loss of an unused exercise reserve.

Sensitive Population Groups

The group with the highest COHb levels in blood are cigarette smokers. However, such individuals should not be considered to be a high-risk group, partly because the baseline hazard is self-imposed (Berlin and Smeets, 1973), partly because the smoker is unable to absorb further CO at normal ambient pressures, and partly because adaptation seems to occur with chronic exposure to high concentrations of CO.

Likewise, workers exposed to high levels of CO have a high blood COHb content on leaving work and are unable to absorb further CO from the atmosphere. Ambient contamination is of significance only in so far as it restricts the elimination of occupationally absorbed CO.

The foetus is more sensitive to CO than the adult, and some of the phenomena observed when a mother smokes throughout pregnancy, such as increased abortion rates, perinatal mortality and impaired intellectual development of the growing child are plainly pathological. If due to CO exposure, we would conclude that the maximum tolerable limit has been exceeded. However, it is not completely certain whether these problems of pregnancy and the puerperium can be atrributed to CO. Conceivably, they could arise from exposure to other constituents of cigarette smoke, or from the socioeconomic status and health habits of a mother who chooses to smoke. In animals, where experiments have been based on exposure to pure CO, the critical dose has been larger than that which results in psychomotor disturbances in the healthy adult (impaired placental function at 7% COHb, foetal death at 15% COHb).

A substantial segment of the population suffers from various forms of hypoxic disease. However, such disease makes an individual more sensitive to CO only if it limits oxygen transport to those tissues vulnerable to CO poisoning (brain, heart and skeletal muscle). The most obvious candidate pathology is cerebro-vascular disease, but to the knowledge of the reviewer no tests have been conducted to determine the CO sensitivity in this type of population. In contrast, there has been considerable investigation of interactions between coronary atherosclerosis and CO exposure. Possible sequelae of CO poisoning include a shortening of the time to exercise-induced angina, a lowering of the threshold for cardiac dysrhythmias and an increase in the likelihood of cardiac death. Angina has been hastened at the COHb level in blood of 1.8% in "passive smoking" experiments (Aronow, 1978), although in such circumstances an effect could have arisen from other constituents of cigarette smoke or from a psychological reaction to cigarette smoke (Table 2). The same laboratory described a shortening of time to exercise-induced angina at a blood COHb level of 2.5-3.0% (Aronow and Isbell, 1973), although somewhat suprisingly symptoms were not accompanied by ECG changes such as ST segmental depression, and there was no other evidence of harm from the CO exposure. A somewhat similar dose of CO (final blood COHb content of 2.8%) hastened the onset and increased the duration of intermittent claudication in patients with peripheral vascular disease (Aronow et al., 1974). All of these reports originated from one laboratory, but welcome confirmation of the alteration in time to angina was provided by Anderson et al., (1973) after a more severe CO exposure (5 Pa for 4 hours, 2.9% increase of COHb). Animal experiments suggest that substantially greater exposures (COHb 8-9%) are needed to induce ventricular dysrhythmias and pathological changes in the myocardium. A blood COHb reading of 2.5-3.0% must nevertheless be regarded as at least a level C exposure (warning level, subjectively unpleasant) for a sensitive group of patients. The proportion of the urban population falling into this category is still hotly debated. Although 20% or more of the population have some degree of ischaemic heart disease, those with sufficient coronary narrowing to be influenced by CO exposure may amount to only 2% of the total population.

Table 2 - Reactions to carbon monoxide in patients with ischaemic heart disease and peripheral vascular disease

Technique	COHb%	Author	Comment
Passive smoking - time to angina	1.8-2.3	Aronow (1978)	Effect could be due to other constituents of smoke or to psychological response to smoke
Double-blind inhalation of CO - time to angina	2.5-3.0	Aronow and Isbell (1973)	No ECG changes
Double-blind inhalation of CO - time to angina	Δ 2.9	Anderson et al.,	No greater effect at 4.5% Δ COHb
Double-blind inhalation of CO - onset and duration of intermittent claudication	2.8	Aronow et al.,	

There are suggestions that a similar level of CO exposure (COHb 2-3%) increases the likelihood of cardiac deaths presumably by increasing the frequency of dysrhythmias (Table 3). If these conclusions are sustained by further investigation, this would set the ultimate limit to urban CO exposure. Levels D and E (increased hospitalization and death) may even be reached with a sustained blood COHb content of ~ 1.4% at sea level (Cohen et al., 1969) and 0.9% at an altitude of 1500 metres (Kurt et al., 1978). Unfortunately, the available data must be accepted with considerable reservations. There is no guarantee that patients developing cardiorespiratory complaints or dying have not been exposed to substantially higher levels of CO than those indicated by a limited number of urban sampling stations. Furthermore, although the authors attributed the regional and seasonal effect to CO exposure, it could have arisen from some other unmeasured factor - a seasonal epidemic or the accumulation of some other air contaminant in the more polluted sectors of the cities studied. In the Los Angeles experiments it is particularly unsatisfactory that much of the observed difference of cardiac fatality rates was due to an improved experience in an area of low pollution, rather than a worsening of rates in the polluted part of the city.

The only positive finding in Baltimore (where CO levels ranged from 0-0.4 Pa) was a high blood COHb level in nonsmokers dying of arteriosclerotic heart disease (Kuller et al., 1975). This was explained as due to an incorrect reporting of smoking habits, since the effect disappeared when ex-smokers were eliminated from the sample.

Table 3 - CO exposure and cardiac deaths

CO pressure	Variable	Authors	Comment
0.8 Pa (7-day average) (~ 1.4% COHb)	Case fatality rate	Cohen et al., (1969)	Seen in winters only - mainly reduced mortality where low pollution
2 Pa (24-hour average) (~ 3.5% COHb)	Excess cardio-vascular deaths	Hexter and Goldsmith (1971)	Allowance for season, temperature and oxidants
<0.4 Pa (24-hour average) versus 0.9 Pa (~ 1.6% COHb)	Sudden death, myocardial infarction, total arteriosclerotic heart disease	Kuller et al., (1975)	No effect except higher postmortem COHb in arteriosclerotic heart deaths (due to subjects describing themselves as ex-smokers)
>-.5 Pa (24-hour average) (~ 0.9% COHb) >1.1. Pa (1-hour average (~ 0.6% COHb)	Cardiorespiratory complaints in emergency room	Kurt et al., (1978)	Population sensitized by altitude > 1500 m?

Other conditions which are associated with increased sensitivity to carbon monoxide are summarized in Table 4. Information on many of the populations listed is very sketchy or nonexistent. All of these groups are undoubtedly more sensitive to CO-induced psychomotor disturbances than are sedentary young adults, but there is as yet no evidence to suggest that they are as sensitive as patients with coronary and peripheral vascular disease in terms of the development of pathological problems during episodes of intense pollution. While more research on such populations would be useful, it does not seem to be a high priority at the present time.

Table 4 - Groups with increased sensitivity to CO exposure

(a) Hypoxic conditions - foetus, anaemia, chronic obstructive lung disease, ischaemic heart disease, peripheral vascular disease, cerebral vascular disease, high altitude residents, elderly.

(b) Hypermetabolic conditions - increased ventilation due to vigorous physical work, pregnancy, high altitude, thyrotoxicosis, newborn infants, hypoxic conditions.

(c) Increased endogenous production - pregnancy, newborn, haemolytic disease, saturation dives, drugs (phenobarbital, diphenyl hydantoin, methylene chloride).

Critical Exposure Level for Sensitive Populations

(a) Physically Active Populations. The critical blood level for the development of impaired psychomotor function is unlikely to be reduced by physical activity; indeed, to the extent that physical activity increases arousal, the threshold of blood level of COHb% may be increased somewhat. On the other hand, the increase of respiratory minute volume allows a more rapid attainment of the limiting COHb level during exposure to transient peaks of pollution. Over periods of one hour or less, activity sufficient to induce a respiratory minute volume of 30 L/min gives at least a threefold increase of COHb readings relative to the normal resting state. The psychomotor threshold of 3 to 4% COHb is thus reached with 15 minutes of exposure to 20 Pa CO, a 60-minute exposure to 5 Pa or an 8-hour exposure to 2 Pa.

(b) High Altitude Dwellers. The interaction between high altitude sojourn and CO exposure is a major public health consideration in the U.S. and in many South American cities. It may also become more important in Canada as Calgary expands towards the Rockies. The effects of altitude and carbon monoxide are additive, although it is less well established that a simple linear addition of response occurs. There may well be a threshold of about 2000 m before altitude induced hypoxia causes a significant impairment of function. The situation is further complicated by the probable acclimatization of permanent high altitude residents to hypoxia.

It is difficult to accept the view of Pitts and Pace (1974) that an ascent of 109 metres results in a 1% increase of blood COHb content except at relatively high altitudes. At most, a 7 to 8% loss of oxygen transport is observed in residents of Mexico City (about 2200 m), and on this basis it could be argued that 300 metres is associated with a change in blood COHb of 1%. Residents of Calgary (about 1050 metres) would then be expected to have a baseline COHb of 3.5% (0.5% endogenous, 3.0% altitude effect) and psychomotor disturbances might be anticipated with very small additional doses of CO. Plainly, there is an urgent need for well-controlled research studies on the CO sensitivity of newcomers to altitudes of 1000-2000 metres.

The situation of the foetus is also worse at 1000-2000 metres than at sea level (a viewpoint supported by public health statistics on birth weights and neonatal mortality). Groups with ischaemic heart disease must be extremely vulnerable to CO if they also live at high altitude. The experiments of Kurt et al., (1975) support this suggestion, since their data showed increased cardiorespiratory admissions to hospital at an estimated blood COHb level of 0.6-0.9%, only slightly above the natural background level.

(c) Endogenous Formation of COHb. Endogenous formation of COHb can be increased up to threefold by conditions such as pregnancy. A threefold increase of endogenous CO would increase the baseline COHb level from 0.5 to about 1.5%. The ambient CO exposure needed to reach the psychomotor threshold of 3 to 4% would remain unchanged at equilibrium, but the quantity of CO needed to reach the critical COHb level would be reduced by a third, causing a 50% increase in sensitivity to brief CO exposures.

(d) Hypoxic Disease. Conditions such as anaemia and chronic obstructive lung disease probably cause some increase in sensitivity to CO by lowering maximum oxygen intake, although there is no good experimental proof of this point. Sensitivity to CO transients is also increased by hyperventilation, and in haemolytic anaemia there is an increased endogenous formation of CO.

(e) Arteriosclerotic Heart Disease. Based on the most pessimistic calculations (Hexter and Goldsmith, 1971), a 24-hour average CO pressure of 2 Pa (3.5% COHb) leads to 11 excess deaths per day in the Los Angeles area. This is equivalent to about 0.7 deaths per 1000 people per year. The vulnerable individuals have severe ischaemic heart disease, a condition that is necessarily costly to treat and has a poor prognosis. It is therefore debatable how much attention public health workers should direct to this problem. Certainly, the risk is substantially smaller than that arising from traffic accidents in a major conurbation, both in terms of frequency of occurrences and years' loss of "useful life". Nevertheless, a level of pollution causing 11 excess deaths in a major city is probably excessive.

Models of CO Uptake

There are substantial differences in the blood COHb concentrations predicted for a given ambient CO level, depending upon the model that is accepted (Table 2) and the anticipated level of physical acitivity of the subjects (Tables 2 and 3). The earliest prediction equations were linear in type, and thus applied only to the early phases of equilibration with exposure

to a given concentration of CO%; over long exposure periods, the COHb% in blood was overestimated. Goldsmith et al., (1963) and Hanks and Farquhar (1969) overcame this problem by using exponential functions. Their approach has been further exploited by Chovin (1974) and Coburn et al., (1965). The equation of Coburn et al., (1965) is widely preferred because it includes many important physiological variables such as the pulmonary capillary oxygen pressure, the O_2/CO affinity ratio for haemoglobin, the oxygen saturation, the pulmonary diffusing capacity, alveolar ventilation, endogenous CO production, blood volume, and total inspired gas pressure. The main disadvantages of the Coburn equation are: (i) calculations must proceed in an iterative fashion (to allow for the interdependence of HbO_2 and COHb) and (ii) the predicted half-time for elimination of CO under resting conditions exceeds that which is observed in practice. Despite these problems, the Coburn equation allows for more factors than the recently proposed equation of Ott and Mage (1978). Discrepancies between the model of Coburn et al., (1965) and other exponential formulae (Table 2) are relatively small during rest and light physical activity, and it must be accepted as the best available procedure for relating ambient CO pressure, exposure times, physical activity, and resultant COHb levels (Table 3).

Choice of Safety Margin

One basic issue in the choice of a safety margin is the severity of the manifestation to be avoided - a substantial margin is justified for carcinogenesis, teratogenesis, and (in the case of CO poisoning) an obvious increase of cardiac fatalities. However, a minor disturbance of vigilance that can be corrected by an increase of arousal is of lesser concern. A second consideration is the universality of exposure (for example, a large safety margin is needed to guard against contamination of drinking water or a staple food product). The general quality of urban air is a problem of similar universality, but local CO contamination of a busy intersection may affect only a small segment of the population. A third variable is the likely variation in human responsiveness to the pollutant. A wider margin of safety is necessary if the criterion is based upon the reaction of healthy young adults than if the limit of exposure has been set by reference to a specific and abnormally sensitive segment of the population (such as patients with ischaemic heart disease). A related issue is retention of the toxic material in the body - some minerals and pesticides have an extremely long half-time, whereas that for inhaled CO is only 3 to 4 hours. Finally, there are questions of economics and practicality. Heavy capital expenditures on new systems of mass transit would be necessary to allow more than marginal changes in urban CO concentrations. The potential safety margin is further circumscribed by naturally occurring sources of the pollutant, and (in the case of CO) by endogenous production.

A 100-fold margin between permitted dose and minimal effect has been proposed for foodstuffs, but this is plainly impracticable for airborne CO. Given the fairly clear evidence of an effect at a blood COHb content of 3%, and an endogenous production equivalent to a COHb level of 0.5%, the safety margin could not usefully exceed a factor of 6. Further, this margin is impossible to attain except for a nonsmoker living in a remote rural area, with no local CO contamination of his dwelling.

A reasonable proposal would be to limit the blood carboxyhaemoglobin content to 1.5%. Except at high altitude, this would give about a twofold safety margin for effects on time to angina and increase of cardiac fatality rate in patients with ischaemic heart disease, and a similar margin on vigilance, and exercise tolerance for healthy young adults. The corresponding CO pressures for a person undertaking heavy work would be less than 5 Pa for 15 minutes, less than 1.5 Pa for 1 hour and 0.9 Pa for 8 hours (Table 3). Plainly, the Canadian "desirable" standards (Table 1) meet these criteria, but the "acceptable" standards leave a negligible safety margin between the attained dose and that giving rise to measurable effects.

It would be reasonably feasible to set an 8-hour limit of 0.9 Pa and a 1-hour limit of 1.5 Pa. The general urban background concentrations of CO in large Canadian cities rarely exceed these levels. In Toronto, for example, hourly readings do not normally exceed 0.5 Pa, and observations greater than 1.0 Pa are a rarity (Wright, 1976). The main limitation of the twofold safety margin is that some classes of individuals such as taxi drivers and street workers are exposed to from 5 to 10 times general urban concentrations for up to 8 hours a day. The remedy for this situation probably lies in a correction of the local pollution (improved ventilation of tunnels, set back of property from the sidewalk, elimination of traffic "bottlenecks") and/or selection of "healthy" workers rather than imposition of a severe general restriction upon urban CO pressures.

In summary, the twofold margin of safety seems appropriate for towns lying close to sea-level. More investigation of the high-altitude problem is desirable, but based on present evidence it would appear that acceptable levels of CO need reducing, possibly by a factor of 2, at altitudes in excess of 1000 metres.

Form and Averaging Times of Air Quality Objectives

Detection of carbon monoxide in ambient air in Canada is usually based upon the long path infra-red analyser accepted as the standard measuring instrument in the U.S. The number of monitoring stations is much smaller in Canada, and there are fewer formal quality control procedures than in the U.S. Nevertheless, good correspondence has been noted between statistics reported by the Ontario Ministry of the Environment and independent sampling from the same locations (Wright, 1976).

Pollutant levels are currently reported for averaging times of 1, 8 and 24 hours. The main argument for addition of a brief averaging period (e.g., 15 minutes) is a possible difference of physiological response to a CO transient. It has been argued that effects upon the cytochrome pigments and intracellular enzymes are particularly likely to occur if CO is administered as a bolus. However, the physiological responses to CO seem remarkably similar for a given blood COHb reading, whether this is induced rapidly or by slow exposure to a moderate concentration of CO. Further, several factors militate against rapid escape of a CO bolus to the tissues, including a finite rate of uptake in the lungs, and an equally slow transfer of CO in the systemic capillaries. With the possible exception of extravascular effects of CO, a bolus has the same effect as any other method of administering an equivalent quantity of the pollutant, since combination with haemoglobin provides an intravascular averaging process. Considering the tremendous volume of data generated by permanent monitoring stations, and the relatively slow fluctuations of urban background CO readings, there is little justification for shortening the minimum averaging period from 60 to 15 minutes. Nevertheless, a case can be made for brief monitoring periods in specific high-risk situations such as tunnels, underpasses, and narrow urban "canyons".

The nature of the statistic to be reported (arithmetic mean, median, geometric mean, or second highest value for a year) remains controversial. Since recording systems are not completely infallible, there is a danger that the arithmetic mean could be biased upwards by occasional erroneously high determinations. The same criticism would apply to a reporting of the highest or the second highest value. The argument advanced for the "second highest value" is that pollution should not be allowed to exceed the safety limit on a significant number of occasions in any given year. In the London "smogs" of 1952 and 1956, it was certainly the peaks of pollution that killed. However, the situation with regard to provocation of a vehicular accident by CO may be different, since emergency traffic situations are occurring on a random basis, and a single peak of CO pollution does not eliminate all vulnerable subjects. In this type of situation, a measure of the central tendency for CO might give more health information than the reporting of an occasional outlying result. Probably, the optimum compromise is to report (i) the median or geometric mean as an overall measure of success in controlling pollution along with (ii) the number of occasions on which the required safety limit is exceeded, this latter statistic providing the primary basis for regulation of pollutant levels. As a general guide, the 8-hour second highest reading is about 8 times the arithmetic mean for a year, and the 1-hour second highest reading is about 12 times the arithmetic mean for the year.

The retention of three levels of reporting (maximum desirable, maximum acceptable, and maximum tolerable) is potentially confusing, particularly when each must be qualified with respect to such variables as altitude and physical activity. Moreover, the justification for conserving three distinct categories seems weak. In view of the overlap between a dose of CO causing mild physiological changes in a healthy person (maximum desirable), exacerbation of symptoms in a patient with angina (maximum acceptable), and an increased death rate in cardiac patients (maximum tolerable), a single objective (maximum permissible level) should be adopted for CO.

As already noted, the limiting blood COHb content is about 3%, and given a twofold safety margin, permissible sea-level exposure limits ("second highest" values) would be as follows:

	Sedentary	Moderate work	Heavy work
1-hour	4.2 Pa	2.1 Pa	1.5 Pa
8 hours	1.0	0.9	0.9
24 hours	0.8	0.8	0.8

On this basis, there would seem to be little basis for retaining the maximum acceptable objective, even for sedentary individuals. However, if a single standard based on "second highest" annual readings were to be specified for general urban pollution, there would be some grounds for moving upwards from the current desirable average to an 8-hour ceiling of 0.9 Pa (reminiscent of the U.S. maximum permissible level).

Whether the 1-hour maximum should be set at the figure for a heavy worker (15 ppm, 1.5 Pa) is more controversial on three counts. Firstly, a sustained high COHb level has adverse effects on cardiac patients, but it is less certain that a brief increase of COHb will cause their demise. Secondly, because the peak CO reading is sustained for only 1 hour out of 24, any increase of case fatality rates will necessarily be an order smaller when considered on an annual basis. Thirdly, hourly measurement increases the probability of detecting outlying values. For all of these reasons, some case could be made for a 1-hour standard of more than 15 ppm (1.5 Pa) although the U.S. figure of 35 ppm (3.5 Pa) is hard to support. Nevertheless, the 1.5 Pa seems practicable for Canadian cities, and it is to be preferred as increasing the margin of safety.

1. INTRODUCTION - A COMMENT ON UNITS

At most points in this review, carbon monoxide (CO) concentrations will be expressed in standard metric units (Pascals and KiloPascals, Pa and kPa). Where appropriate, results expressed in other terms (for example, % CO by volume, parts per million, or mg per m^3) have been converted to this standard format. For most purposes, 10 ppm = 1 Pa = 11.5 mg per m^3.

More care must be observed in conversion at altitude and in submarine exploration owing to changes of the total barometric pressure. A given partial pressure (measured in Pascals) or mass concentration is equivalent to a higher concentration by volume at altitude than at sea level. Again, a diver may inhale mixtures where the mass concentration of air tested at sea level has been increased sixfold by compression. In the Canadian context, a drop in temperature to -30°C can also convert a concentration of 35 mg/m^3 from 30 ppm to 24.6 ppm, due to the increase in density of the ambient air.

Since biological scientists have opted for standard metric units, these are the preferred method of reporting data. From the viewpoint of air quality and toxicity, the rate of uptake of CO depends largely upon partial pressure, but its success in combining with haemoglobin and cellular pigments depends also upon the partial pressure of oxygen. In chronic exposures at unusual ambient pressures, and in situations where oxygen pressures are low (for instance, fire fighting) account must be taken of both CO and oxygen pressures.

2. HISTORICAL PERSPECTIVE

According to Greek legend (Fischer, 1967), Prometheus stole fire from Olympus and gave it to man as a symbol of knowledge and progress. From that time man must have been at least partially aware of the adverse effects of combustion. The first writings on the effects of carbon monoxide on health are attributed to the Greek philosopher Aristotle, who lived in the third century B.C. (Lewin, 1920). In ancient Rome, the fumes of charcoal were used to commit suicide, and by the time of Cicero (106-43 B.C.) criminals were executed by exposure to charcoal fumes (Cooper, 1966; Lewin, 1920).

The combustion of coal for domestic heating increased during the fifteenth century, and cases of domestic carbon monoxide (CO) poisoning showed a parallel rise (Air Pollution Control Association, 1970). Deacon (1616), in writing of the evils of tobacco smoke, also recognized harmful constituents of coal smoke: "chimnies (by our Ancestors formerly invented), that thereby, the smoke... might be dispersed abroad in the aire, for feare of hurting the bodies of men". More recent reports of high CO concentrations in primitive dwellings during the cooking of food (Sofoluwe, 1968) illustrate that the poorly ventilated combustion of many fuels is potentially dangerous.

In the sixteenth century, coal was recognized as an important national asset and underground mining flourished. A risk of industrial CO poisoning was one consequence of this development, since the gases encountered (termed "damps" from the middle German dampf or vapour) often included quite high concentrations of CO. During the nineteenth century the hazard of industrial and domestic CO poisoning again increased, with the introduction of such manufactured gases as illuminating gas or coal gas (7.4% CO by volume), producer gas (33.5% CO by volume) and water gas (43.6% CO by volume) (Munro, 1964). In the present context, this literature provides some evidence of human responses to chronic CO poisoning. Attempting to reduce the frequency of accidental CO poisoning, the manufacture of gases containing 30 or more per cent CO was discontinued in Great Britain (Haldane and Priestley, 1935). During World War II, the conversion of many European vehicles to producer gas revived interest in chronic CO poisoning (Grut, 1949; Petri, 1953). The use of manufactured gases continued in some parts of New York City until 1956 (Eisenbud and Ehrlich, 1972), and in England until the discovery of natural gas in the North Sea in the 1960's.

While carbon monoxide poisoning is still a cause of fatalities (Beard, 1969; Dale, 1973; DuBois, Zdrojewski and Monkman, 1966; Zikria et al., 1972) and remains an interest of clinicians (Croton, 1959; Douglas et al., 1961; Douglas et al., 1962; Editorial, 1959; Killick and Marchant, 1959; Norman, Douglas and Smith, 1966; Otis, 1970; Zoru and Druger, 1969), the concern in the early part of this century shifted to occupational CO exposures (Cooper, 1966). It is now well

documented that specific occupational groups such as fire fighters (Goldsmith, 1970; Gordon and Rogers, 1969; Gregory, Malinoski and Sharp, 1969; Loke et al., 1976; Radford et al., 1976; Sammons and Coleman, 1974), mine workers (Haldane and Priestley, 1935; Notov, 1959; Rodgers, 1926), traffic policemen (Balabaeva and Kalpaznov, 1974; Chovin, 1967; DeBruin, 1967; Goldstein et al., 1975, Göthe et al., 1969; Wilson et al., 1926), street workers, delivery men and taxi drivers (Godin et al., 1972) forklift operators (Breysse and Bovee, 1969; Goldsmith, 1970; Petrov, 1968), ice rink attendants (Johnson et al., 1975), vehicle inspectors (Catcott and Xintaras, 1962; Cohen et al., 1971a; Johnson et al., 1974; Sievers et al., 1942), parking garage attendants (Buchwald, 1969; Fristedt and Akesson, 1971; Ramsey, 1967), submariners (Bondi et al., 1978), iron foundry and steel-mill operatives (Butt et al., 1974; Davies, Jones and Warner, 1965; Ejam-Berdyer, 1973; Farmer and Crittenden, 1929; Hernberg et al., 1976; Jones and Walters, 1962; Morel and Szemberg, 1971; Virtamo and Tossaveinen, 1976), workers in petroleum and chemical industries (Stewart et al., 1972), and livestock producers (National Center for Disease Control, 1973) can be exposed repeatedly to quite high doses of carbon monoxide (blood carboxyhaemoglobin (COHb) levels of 5-10%, even in nonsmokers). Such occupational burdens influence air quality criteria in two respects - exposure at work augments the 24-hour dose of CO, and high urban readings slow the elimination of CO after leaving work.

While there remain specific concerns regarding the amounts of CO in the working and the domestic environment (Yocom, Clink and Cote, 1971), the scope of investigation has now widened to consider the effects of ambient city air upon the general population. The main reason for this broader concern is the increased use of the internal combustion engine for urban transportation (Bowne et al., 1971)

3. ANALYTICAL METHODS

It is self-evident that no program of air quality control can be effective unless there are good methods for measurement of the pollutant in the urban environment and for an assessment of the cumulative dosage in affected citizens. The last few years have seen considerable advances in techniques for recording ambient CO and blood COHb concentrations, but a continuing multiplicity of methods underscores residual difficulties.

3.1 Determination in Ambient Air

3.1.1. Analysis

Considerations influencing the current choice of methodology include specificity, linearity of response, interference from contaminants, reliability of calibration, ruggedness, portability and cost (Radford and Rodkey, 1973). Ratings of detector performance should also note sensitivity, response time, and accuracy relative to true gas concentrations (Air Pollution Control Association, 1970). "Spot" measurements are sometimes useful in surveys, but because of the chronic and cumulative nature of CO poisoning, continuously recorded data are of greater value.

The U.S. Environmental Protection Agency (1975) now distinguishes clearly between "reference" and "equivalent" methods for the measurement of all atmospheric pollutants, the reference method for CO being the non-dispersive infra-red analyzer. There is also insistence upon adequate calibration standards and quality control procedures. Primary standards are prepared gravimetrically, and are stored in stainless steel or aluminum oxide coated aluminum cylinders; accuracy is within less than 1%, but costs are unfortunately high. The commercial gas mixtures used in many investigations have an accuracy of 2% or worse (Elwood, 1976, cited by Environmental Criteria and Assessment Office, 1979) when purchased, reaction with the cylinder wall leading to a further deterioration of composition if the gas mixture is stored (Hughes, 1975; Wechter, 1976, cited by Environmental Criteria and Assessment Office, 1979). Other technical possibilities include volumetric gas dilution, permeation tubes, and the thermal decomposition of nickel tetracarbonyl; however, the last procedure is not strictly stoichiometric.

Many of the early reports are based upon tedious and rather imprecise chemical procedures for CO determination - the discolouration of palladium-molybdeum indicator tubes (Shepherd, 1947; Shepherd, 1955) and the formation of CO_2 and iodine by passage of the CO overheated iodine pentoxide (Teague, 1920) or a combination of iodine pentoxide, selenium dioxide and sulfuric acid (Silverman and Gardner, 1965; Stewart and Stolman, 1961). With this approach, interference could arise from the other reducing agents,

including acetylene, hydrogen sulfide and hydrogen gas. Early electrochemical devices detected the heat produced when a steady flow of gas was passed over hopcalyte (Linderholm, 1965; Sjöstrand, 1948a), used a galvanic cell to detect the iodine liberated from iodine pentoxide (DuBois et al., 1966; Haagen-Smit, 1966; Hersch, 1964), or made photometric measurements of the halogen liberated from a palladium halide (Allen and Root, 1955a; Le Moan, 1952), the molybdenum blue released from a compound of palladium chloride and phosphomolybdic acid (Polis, Berger and Schrenk, 1944), the coloured complex formed from palladium and nitroso-β-naphthol (Fabre, Truhaut and Boudène, 1952) or the mercury vapour obtained from mercuric oxide (McCullough, Crane and Beckman, 1947). One mercuric oxide method has been developed for continuous gas analysis (Seiler and Junge, 1970). A later form of electrochemical detector is the "Ecolyser" (Bay et al., 1972; Bay et al., 1974; Blurton and Bay, 1974; Yamate and Inoue, 1973); a catalytically active electrode converts CO to CO_2, and this is measured in terms of the associated hydrogen ion production. The apparatus is small and portable (4.1 kg, battery operated), making it an attractive device for "spot-checks" of CO levels on streets and in buildings. Early reports claimed minimal interference from temperature, humidity and other air contaminants (Bay et al., 1972), but some authors have now described a response to organic vapours such as alcohol, acetylene and ethylene, a possible problem in both bars and exhaust-contaminated streets. Tests with pure gas mixtures show a close correlation with gas chromatograph data (Ayres, 1974). One practical limitation of the equipment is a lack of instantaneous response (90% response time 10 sec, decay time ~ 20 sec, Bay et al., 1972).

The most successful devices for continuous monitoring of CO are based on physical principles (Strange, Ball and Barnes, 1960). However, such instruments are usually cumbersome, require a stabilized AC voltage, and can be damaged by vibration or frequent movement. They are therefore usually operated at fixed sampling sites. Non-dispersive infra-red analyzers are the primary reference method, and are now used quite widely for environmental monitoring (Air Pollution Control Association, 1970; Pierce and Collins, 1971). A very long absorption path and/or high pressure analysis is necessary to give the required sensitivity (Hill and Powell, 1968; Jacobs, Braverman and Hockheiser, 1959); this slows the response speed and/or increases the sample volume. Technical improvements have substantially increased the accuracy of this type of equipment over the past 15 years. Developments include the use of twin-beam instead of single beam operation, incorporation of signal linearizing circuits, improved thermostats to regulate the source signal and automatic zero and span adjustments. Nevertheless, problems can still arise. The sample inlet should be tested for possible leakage and alteration of gas

composition (CO is easier to handle than some pollutants, in this respect). A particulate filter is needed to protect the analyzer from clogging, but this can affect the signal by causing a pressure drop in the detector chamber. The optical filters used in modern machines largely eliminate a response to CO_2 and water vapour, but screening may be incomplete (Coburn et al., 1964a). Readings are also influenced by oxygen pressure (the "collision-broadening phenomenon", Hill and Powell, 1968). These criticisms are important when examining respiratory gas, but have less relevance when monitoring ambient air. Possible developments of infra-red techniques include second-derivative spectrometry (Lawrence Berkeley Laboratory, 1973), Fourier transform spectroscopy (Haust et al., 1973) and gas filter correlation spectroscopy (Burch et al., 1976). The last instrument has the advantage of eliminating interference from CO_2 and water vapour.

Gas chromatograpy is sometimes used to separate carbon monoxide from other air constituents. A single column packed with silica gel (Szulcewski and Higuchi, 1957), silica gel and iodine pentoxide (Smith, Swineheart and Lesnini, 1958), zeolite (Kyryacos and Boord, 1957) or a molecular sieve (Forster, 1969a) is adequate for this purpose, although better results may be obtained by twin columns - a silica gel to retain CO_2, followed by a molecular sieve to separate the CO (Commins, 1975). Problems of low CO concentrations can be overcome by the use of capillary columns and a sensitive flame ionization detector (Ettre, 1961; Porter and Volman, 1962; Rodkey, 1970). Nevertheless, gas chromatographs are more difficult to operate than non-dispersive infra-red analyzers; stability of carrier gas flow, consistent oven and detector temperature, and consistent sample injection pattern are all mandatory for satisfactory results. Their role, if any, is in the analysis of blood specimens rather than the gas phase (Maisels et al., 1971; Rodkey, 1970).

One of the best current procedures for the analysis of many gases is mass spectrometry. However, there are several disadvantages in using this technique for carbon monoxide (Forster, 1969a) - (i) since the apparatus requires a near vacuum, it is inaccurate when detecting gases in low concentration, (ii) carbon monoxide tends to be produced in the ion-generating section of the apparatus, and (iii) expensive modifications are necessary to distinguish carbon monoxide from nitrogen (which has the same molecular weight).

3.1.2 Sampling Networks

The usual approach to urban sampling is the use of a limited network of long twin-bean, infra-red analyzers; indeed, in the U.S. these have become the standard instruments against which other procedures are evaluated. The detectors are not readily moved, and in the U.S. the total number of sampling sites has increased slowly from 212 in 1973

to 456 in 1977 (U.S. Environmental Protection Agency, 1978). Monitoring stations are generally placed at fixed sampling sites; inlet probes are at a height of 3 metres to avoid vandalism (Altshuller et al., 1966), and at least 1 metre from adjacent structures to avoid frictional and eddy effects (Nickolson, 1975). The U.S. Environmental Protection Agency (1971) recommended a minimum of one station for a city of 100 000 population, with an additional 0.15 sites for each further 100 000 population.

The scale of representativeness of the data depends on the proximity of the probe to a major traffic route. Microscale measurements may be made to judge local compliance with air quality standards or specific hazards to pedestrians, but larger scale measurements are needed to gauge regional pollution trends and diffusion of CO from urban to rural areas. In Canada, the tendency has been to site sampling inlets away from traffic. The concentrations then recorded (0.3 to 1.0 Pa) indicate general background CO levels (Colucci and Begeman, 1969; Hamming, MacPhee and Taylor, 1960; Moureu, 1964; Ott and Eliassen, 1973) rather than the concentrations to which most people are exposed in specific areas of a metropolis (Brice and Roesler, 1966; Godin, Wright and Shephard, 1972; McCormick and Xintaras, 1962; Wilkins, 1956; Wright et al., 1975). For certain occupational groups (such as taxi drivers) microscale readings may provide a better indication of exposure patterns.

The interpretation of data is influenced by the method of detector calibration; for example, in the U.S., a change from mono to twin-beam detectors and substitution of air/CO for N_2/CO calibration mixtures led to a substantial drop in reported CO concentrations (Tiao et al., 1975). Figures also depend upon the reporting period (hourly, daily or seasonal). The sampling sites may have identical mean readings, but substantial differences in extreme readings. Most city monitors indicate morning and evening rush-hour peaks (Brief et al., 1960; Colucci and Begeman, 1969), with a sustained evening rise due to increased atmospheric stability (Godin et al., 1972). Super-imposed upon this diurnal rhythm are seasonal variations in CO production and atmospheric stability, plus local geographic factors that influence the development of thermal inversions (Shephard, 1974). Data are often reported as the arithmetic mean, but this is too heavily influenced by occasional aberrent values; the median and the geometric mean are more appropriate statistics for what is usually a log-normal distribution. Air quality standards may require the reporting of the highest or the second highest value over a specified year, using a moving average rather than a fixed time span such as 12:00-8:00 a.m. (McMullen, 1975). In the event that there are missing data, this can still be estimated from a frequency

distribution for the available CO readings. However, more sophisticated statistical treatment of observations is complicated by the auto-correlation of data for successive time intervals.

3.2 Determination in Biological Tissues

3.2.1 Blood Phase

Direct estimation of carbon monoxide in the blood phase may be made on venous or arterial specimens, since the arterio-venous CO difference is normally insignificant. The sampling tube must be air-free. Carbon monoxide may be liberated and analyzed by a similar range of techniques to those discussed above (Commins, 1975). If the blood carboxyhaemoglobin content is to be estimated from the data, it is important that samples be well mixed. The classical Van Slyke manometric procedure used an acid ferricyanide procedure to release CO, CO_2, O_2 and N_2; CO was estimated as a residual gas pressure (Van Slyke and Neill, 1924) or a pressure change subsequent to absorption in cuprous chloride (Sendroy and Liu, 1930). However, the analysis was lengthy (Gettler and Mattice, 1933) and until the introduction of microgasometric techniques (Allen and Root, 1955b; Linderholm, 1965; Scholander and Roughton, 1942; Scholander and Roughton, 1943) substantial samples of blood were required.

Subsequent authors extracted CO by the Van Slyke mercury pump, but relied on a chemical (Ammundsen and Grut, 1943; Christman and Randall, 1933; Rice, 1952; Wennesland, 1940) or a physical (Gaensler et al., 1957; Lawther and Apthorp, 1955; Moureau et al., 1957) rather than a volumetric or manometric determination. An accuracy comparable with the classical Van Slyke procedure was claimed, but methods were still time-consuming and demanded considerable experience. Investigators have coupled the gas chromatograph to manometric extraction of CO (Ayres, Criscitiello and Giannelli, 1966; McCredie and Jose, 1967). More recently, vortex extraction has been adopted (Dahms and Horvath, 1974), this method allowing 100 µL samples of blood to be analyzed with a coefficient of variation of 1.7%.

Conway (1950) developed a chemical procedure whereby CO was liberated from haemoglobin in a microdiffusion cell, using sulphuric acid. The CO was then absorbed by palladium chloride, and released hydrogen ions were titrated with a microburette. The method was accurate but tedious, and required 2 µL samples of blood.

Biological estimates are based on differences in the spectra of haemoglobin, oxyhaemoglobin, and carboxyhaemoglobin. Haldane (1895a) attempted to match the cherry red colour of COHb with standard blood specimens to which he had added known amounts of a carmine dye. However, problems arose from variations in the amount of daylight

illuminating the tubes (Haldane, 1895b). The COHb also tended to dissociate in strong sunlight (Haldane, 1896), haemoglobin levels varied between subjects (Haldane and Smith, 1898) and the COHb reaction was affected by room temperature (Hartridge, 1912b). It was generally agreed that the method was inaccurate, except in Haldane's hands, and it may have led him to various erroneous conclusions (Grut, 1949; Hartridge, 1912a).

A single beam spectroscopic method was introduced by Hufner as early as 1889 (Hartridge, 1912a), and the twin-beam reversion spectroscope is due to Hartridge (1912a,b). The latter works quite well at high COHb levels (Douglas et al., 1962), but lacks sensitivity below 35% carboxyhaemoglobin saturation (Commins, 1975). More recently, spectrophotometric methods have been adopted. These have the advantage that small or very small samples (10 µL to 0.5 µL) of blood are required, but interference can occur from other pigments such as methaemoglobin and myoglobin. Haemolyzed blood is commonly treated with a reducing agent such as sodium thiosulphite; the proportions of Hb and COHb can then be determined from the relative absorption of light at two suitable wavelengths (Harper, 1952; Paul and Theorell, 1942). Klendshøj, Feldstein and Sprague (1950) compared various possible wavelengths, and concluded that data obtained at 480 and 555 mµ gave the best correlation with Van Slyke results. Others compared the observed absorption with that obtained after full oxygenation (Commins and Lawther, 1965; Lily, Cole and Hawkins, 1972), exploited the slow conversion of COHb to methaemoglobin (Paul and Theorell, 1942), or the less ready heat precipitation of COHb relative to HbO_2 (Whitehead and Worthington, 1961). Linderholm, Sjöstrand ans Söderström (1966) and APCA (1970) concluded that none of the available spectrophotometric methods were of sufficient sensitivity for monitoring the normal blood COHb% of urban inhabitants. However, Lily et al., (1972) subsequently claimed a standard deviation (S.D.) of only 0.13% for COHb levels less than 3%.

By coupling an absorption spectrophotometer to an analogue computer, it is now possible to make measurements of COHb, HbO_2 and Hb on a single blood sample (Mass, Hameliak and de Leeuw, 1970; Malenfant et al., 1968). Measurements of absorbance are made at 3 wavelengths (548, 568 and 578 mµ) and the analogue solves the 3 corresponding simultaneous equations. The S.D. of COHb% estimated by this method is 0.4% (Mass et al., 1970), although frequent calibration is required to ensure valid results (Cole, 1973). Another procedure (Small et al., 1971) uses a precision spectrometer to make measurements at 4 wavelengths in the near-ultraviolet; the procedure is rapid, requires 100 µL blood samples, and has an accuracy of ± 0.6% COHb.

Spectrophotometric methods, like the bloodless methods to be discussed below, have the advantage that the value reported is COHb% rather than blood CO content. To convert CO content to COHb%, it is necessary to obtain an accurate haemoglobin reading, and to assume a fixed stoichiometric relationship of CO and haemoglobin; such an assumption is probably warranted for well-mixed blood, although it has been disputed (Lauwerijs, 1973).

3.2.2 Bloodless Methods

Blood sampling is unpopular with volunteers, and for this reason bloodless methods of determining COHb have become quite popular, particularly in urban and industrial surveys. The majority are based on a rearrangement of Haldane's equation:

$$COHb\% = HbO_2\% \; M \frac{P_{CO}}{P_{O_2}}$$

Equilibrium is established between alveolar and pulmonary capillary gas by a period of oxygen rebreathing. It is then possible to assume that $HbO_2\%$ is ~ 100; P_{CO} and P_{O_2} can be measured in the rebreathing bag, and a standard value can be assumed for M (Dahlström, 1955; Henderson and Apthorp, 1960; Sjöstrand, 1948a,b). Criticisms of the procedure include (i) incomplete equilibrium between gas and blood phases; (ii) non-uniformity of alveolar CO (particularly in patients with chronic chest disease); (iii) hyperventilation due to accumulation of CO_2 in the rebreathing system (Grut, 1949); (iv) changes in gas composition in the rebreathing bag (overcome by use of an aluminized mylar bag), and (v) individual differences in values of M (Dahlström, 1955). The last criticism is perhaps the most serious. Although some authors have found almost constant values of M, Dahlström noted figures ranging from 228 to 413; interestingly, in his experiments, M was more constant (218-229) for the formation of additional quantities of COHb%. Carlsten et al., (1954) found M to have a standard deviation of ± 45. Rodkey et al., (1974) estimated that M had a value of 220 to 250 at physiological pH and body temperature. Roughton (1970) reported an average value of 246, but stressed that this varied over differing segments of the oxygen dissociation curve.

Despite problems from an uncertain figure for M, comparison of the rebreathing method with more direct methods of measurement has shown good agreement, the slope of the COHb%/alveolar CO line having the expected value of 0.155 (Coburn et al., 1965; Forbes et al., 1945; Sjöstrand, 1948a,b). Henderson and Apthorp (1960) used a rebreathing method with preliminary nitrogen washout, and found all but two of such observations fell within 10% of the line of identity relating them to direct blood determinations. Hackney et al., (1962) omitted the nitrogen washout stage of the rebreathing procedure,

but still found a coefficient of variation of only 4.4% for their indirect estimates (5.0% if the oxygen content of the rebreathing bag was assumed rather than measured).

R.H. Jones et al., (1958) proposed the even simpler approach of 20 sec breathholding, following a maximal inspiration from functional residual volume. The COHb% predicted from alveolar P_{CO} at high COHb% readings again fell within 10% of the directly measured value in 90% of samples. Although their data showed disproportionately large increments of alveolar P_{CO} at high COHb% readings, this point was not confirmed by Ringold et al., (1962) or McIlvaine et al., (1969). The technique becomes inaccurate if there is a high atmospheric concentration of CO and the subject has not yet equilibrated with his environment (Peterson, 1970). Several linear and quadratic equations for the prediction of COHb have been proposed, based on equilibration studies at low ambient partial pressures of CO:

$$\text{COHb\%} = 1.8\,(\text{CO Pa}) \quad \text{(McIlvaine et al., 1969)}$$

$$= 1.4\,(\text{CO Pa}) + 1.09 \quad \text{(Goldsmith, 1965)}$$

$$= 1.6\,(\text{CO Pa}) \quad \text{(Goldsmith and Landaw, 1968)}$$

$$\text{CO (Pa)} = 0.014\,(\text{COHb\%})^2 + 0.31\,(\text{COHb\%}) + 0.42 \quad \text{(Peterson, 1970)}$$

4. SOURCES

4.1 Natural Sources

Carbon monoxide is produced in volcanic, marsh and natural gases and during electrical storms (Jaffe, 1968). Small quantities of CO are also formed by seed germination, seedling growth (Seigel, Renwick and Rosen, 1962) and injured, cut or dried green vegetation such as crop plants, shrubs, grasses, weeds and algae (Wilks, 1959). Carbon monoxide is produced and trapped in the float cells of marine hydrozoan jellyfish (Barham and Wilton, 1964) and in the bladders of a number of marine brown algae (Chapman and Tocher, 1966). The world's oceans may thus contribute CO equalling 5% of that generated by combustion of fossil fuels (Swinnerton, Linnebom and Lamontagne, 1970).

Anthropogenic atmospheric emissions of CO are apparently increasing. Extrapolating from the calculations of Bates and Witherspoon (2952), Robbins, Borg and Robinson (1968) estimated that in 1968 man produced 2×10^{14} grams of CO (200 million tons). By 1972, production has risen to 270 million tons per year, more than half of the CO content of the troposhere, which was estimated by one author (Maugh, 1972).

The relative importance of natural and man-made CO production is still debated. According to some authors, natural formation from methane (McCormick and Xintaras, 1962) contributes 10 times the anthropogenic output (Coburn, 1979; Jaffe, 1973; Levy, 1973; Maugh, 1972; McConnell et al., 1971). This would cast doubt on the importance of global measures for the control of air quality. Other calculations, based upon the distribution of various CO isotopes in the atmosphere (Crutzen and Fishman, 1977; Seiler, 1978; Stevens et al., 1972) have restored belief in the primacy of man-made CO. Certainly, the global burden of CO is increasing systematically, with long-term implications for stratospheric photochemistry, including the stability of the ozone layer. Furthermore, human activity is clearly responsible for the high urban CO concentrations that are of significance to health. Rural CO levels are typically no more than 0.003 Pa to 0.08 Pa, depending on exposure to local and continental air masses (Robbins et al., 1968; Junge, 1963). Somewhat higher figures are observed if the air mass traverses a major conurbation. The global average for the troposphere is estimated at 0.01 Pa CO, (0.014 Pa for the Northern Hemisphere and 0.006 Pa for the Southern Hemisphere) (Robinson and Robbins, 1970); partial pressures drop to 0.008 Pa at an altitude of 4 km and 0.004 Pa at 15 km (Goldman et al., 1973).

Despite rising CO output, background levels of CO in the lower atmosphere remain relatively stable. There must therefore be some atmospheric removal process (Jaffe, 1968). The reaction $CO + OH \rightarrow CO_2 + H$ is one possible mechanism (Hampson and Garvin, 1975;

Weinstock, 1969). More significant removal occurs at the earth's surface; anaerobic soil bacteria oxidize CO to CO_2 in the absence of H_2 or reduce CO to methane in the presence of H_2 (Inman, Ingersoll and Levy, 1971). The residence time of tropospheric CO is thus no more than 0.2 years (Weinstock et al., 1972, 1974).

4.2 Anthropogenic Sources

4.2.1 Automotive Emissions

Vehicle exhaust is the principal man-made source of CO. As one of the products of the internal combustion engine, CO is discharged into the atmosphere along with water, carbon dioxide, nitrogen, hydrogen, nitric oxide and hydrocarbons (Hurn, 1962). Diesel engine exhaust generally contains less than 0.1% CO (Elliott, Nebel and Rounds, 1955), whereas carburetted engines emit some 4% by volume of CO (Chipman and Massey, 1960; Elliott et al., 1955; Hurn, 1962; Larson, Chipman and Kauper, 1955; Twiss et al., 1955). The exhaust volume depends on engine speed, while the CO concentration depends mainly on the air to fuel ratio (Air Pollution Control Association, 1970). Diesel engines normally operate with a substantial excess of air (Elliott et al., 1955). Fuel-rich operation increases the concentration of CO in both diesel and carburetted exhaust (Twiss et al., 1955). For example, relatively high contaminant emissions per vehicle-km are associated with business routes which require much stop and start driving; on the other hand, freeway driving at cruising speeds of 70-100 $km \cdot h^{-1}$ produces quite low contaminant emissions per vehicle-km (Rose and Smith, 1962; Rose et al., 1965).

Engineering improvements have reduced the CO emissions from a typical vehicle by 70% compared to the "uncontrolled" car of 1960. The total estimated automotive emissions for the U.S. have thus fallen 17% from their 1967 level of 90×10^9 kg per year (Bowditch, 1972). This reduction has been attained mostly by maintaining an increased air to fuel ratio (approximately 14.5 to 1) in all modes of operation (Air Pollution Control Association, 1970). A number of factors may increase emissions from supposedly improved vehicles. Firstly, pollution control devices are tested on new, well-tuned engines. It is difficult to sustain acceptable emission limits beyond 15 000 to 18 000 km of operation (Chass et al., 1972) and the increased maintenance required by pollution control devices is not generally recognized by the motoring public. About 70% of the vehicles checked in one large North American city had not been adequately maintained (Winthrop, 1972). Another problem, particularly from a Canadian perspective, is the increased emissions from a cold engine (Hurn, 1962); CO produced during the first few minutes after start-up (as in many short urban trips) comprises an important fraction of total emissions (Hass and Brubacher, 1962). Driving patterns are also affected by

snow-covered roads, while winter driving conditions cause emission control systems to deteriorate quickly (Winthrop, 1972). Carbon monoxide emissions increase with altitude, since the decreased atmospheric partial pressure of oxygen results in less complete combustion (Larsen and Konopinski, 1962). Motor vehicle use may well continue to increase in major conurbations, and even if fuel shortages permit the sequential introduction of more effective control devices, these may do little more than maintain the status quo (Goldsmith and Landaw, 1968) of emission statistics. Finally, it must be stressed that evaluation of air pollution control devices has relied on statistics for gross emissions, thereby neglecting the most critical area-population exposure in the cities (Sweet, Steigerwald and Ludwig, 1968).

Street level CO concentrations are influenced by wind speed and direction, atmospheric stability, immediate traffic density and the height of nearby buildings. Typical concentrations are likely to range from 1 to 5 Pa (Bové and Siebenberg, 1970; Brice and Roesler, 1966; Georgii, Busch and Weber, 1967; Godin et al., 1972; Ontario Ministry of the Environment, 1972; Ramsey, 1966; Wilkins, 1956; Wright et al., 1975) with much higher readings (5 to 20 Pa) in such sites as overhanging entrances, poorly ventilated tunnels and underpasses and underground garages (Ayres et al., 1973; Bithel, 1970; Conlee et al., 1967; Lawther, Commins and Henderson, 1962; Miranda et al., 1967; Ramsey, 1967; Rispler and Gilbert, 1970; Wilkins, 1956; Wright et al., 1975). The motorist who drives with his windows closed encounters less variable CO concentrations (1 to 2 Pa) than the pedestrian (Chaney, 1978; Clayton, Cook and Frederick, 1960; Godin et al., 1972) or the cyclist (Kleiner and Spengler, 1976). However, when the windows are open, the buffering effect of his cab is lost and higher (2 to 5 Pa) levels are obtained (Brice and Roesler, 1966; Haagen-Smit, 1966).

The CO levels within offices and homes lags behind outdoor concentrations, and some of the sharper peaks of pollution are not seen (General Electric, 1972; Schaplowsky et al., 1974; Yocum et al., 1971). Nevertheless, CO differs from many pollutants in that it has little tendency to become absorbed on walls and fabrics, so that equilibrium between indoor and outdoor air can be reached relatively quickly. Indoor concentrations may exceed ambient levels if one of the occupants is a smoker, or there are other local sources of carbon monoxide such as stoves, heaters, or leakage from an attached garage (Benson et al., 1972; General Electric Company, 1972).

4.2.2. Tobacco Smoke

Since tobacco smoke is formed by slow combustion, its relatively high CO content is not surprising (Dudley, 1888; Gettler and Mattice, 1933). Dudley (1888) realized that

although CO_2 was first formed as the air was drawn through the "layer of fire", the hot carbon residues reduced the CO_2 to CO. Wahl (1899) was the first to determine the CO content of pipe and cigar smoke, finding respective partial pressures of 2.3 and 6.2 kPa. Armstrong (1922) suggested that the closeness of packing of tobacco and the rate of smoking modified the CO pressure (0.9 to 1.2 kPa for cigarettes, 1.1. kPa for pipes and 5.8 kPa for cigars); concentrations recorded in his study for the CO content of the smoke of cigarettes and pipes are somewhat lower than those found in more recent studies.

While Baumberger (1923) mentioned "burning point" smoke, it was Bogen (1929) who introduced the now accepted terms of "mainstream" for the smoke drawn through the cigarette and "sidestream" for the smoke escaping from the burning end. Today the term sidestream smoke also includes smoke escaping from the mouthpiece during puff intermission (Wynder and Hofffmann, 1967) and the small volume that diffuses laterally through the cigarette paper (Hoegg, 1972). The average cigarette smoker takes a 35 mL puff of mainstream smoke over an interval of 2 seconds, at a rate of one puff per minute (Guillerm et al., 1972; Mumpower, Lewis and Touey, 1962); this has been compared with exposure to 40 to 50 Pa of CO throughout the period of smoking (about 6 min).

Early analyses of cigrette smoke required a sample volume of 100 mL, and thus the smoking of several cigarettes (Osborne, Adamek and Hobbs, 1956). However, gas chromatography (molecular sieve column) has allowed CO determinations in a single puff. Mumpower et al., (1962) found a minimum CO pressure in the third puff of an unfiltered king size cigarette (3.1 kPa), an intermediate value (4.4 kPa) in the eighth puff and the maximum value in the thirteenth puff (5.0 kPa). The average CO concentration increased with puff volume, corresponding figures for a 60 mL puff being 4.8 kPa, 5.3 kPa and 7.7 kPa. The CO yield of 15 brands of commercial cigarettes were compared. There were no major differences between filter and nonfilter cigarettes, nor between king size and regular cigarettes at a standardized butt length. However, the CO delivery per puff tended to be higher for regular size than for king size cigarettes during the initial puffs (Newsome and Keith, 1965; Robinson and Forbes, 1975).

Hoffman and Wynder (1972) investigated specific compositional differences between the smoke from cigarettes, cigars and the newer "little" cigars. All three products were machine-smoked to give a 35 mL puff of 2 seconds duration once every minute, although it is debatable whether cigars are smoked in this way. The CO pressure in the mainstream smoke of one brand of little cigar (5.3 kPa) was comparable to that of cigarette smoke

(4.5 kPa). However, the smoke from another brand of little cigar and a small cigar yielded the high CO readings of 11.1 kPa and 7.7 kPa respectively. The CO concentration of cigarette sidestream smoke averaged 4.7 times that for mainstream smoke (Bridge and Corn, 1972; Hoegg, 1972).

These statistics have several important implications in air quality control. Firstly, the amount of CO that the average smoker absorbs from tobacco products is far greater than the amount received from the urban atmosphere; indeed in most instances atmospheric contamination does no more than impede elimination of tobacco-generated CO. Secondly, the heavy smoker is partially acclimatized to CO poisoning, and may respond differently than a nonsmoker when an experimental dose of CO is administered. Unfortunately, many experimental protocols fail to distinguish smokers from nonsmokers. Finally, accumulation of cigarette smoke in a poorly ventilated room adds considerably to the normal urban exposure to CO (Sebben et al., 1977).

The smoke found in enclosed spaces consists of all the sidestream smoke and that part of the mainstream smoke which has not been absorbed in the smoker's mouth or lungs. The extent to which nonsmoking individuals are exposed depends on the proximity of smokers, the amount and type of smoke they produce, the volume and ventilation of the room and any local obstructions to ventilation (Steinfeld, 1972). The pattern of smoking influences both the composition of exhaled smoke and the proportion of sidestream smoke produced per cigarette. One cigarette smoker in an office-sized room can produce an average CO concentration of 1 Pa (Harke, 1970), although concentrations are higher (2 to 3 Pa) in close proximity to the smoker (Dublin, 1972). CO concentrations of from 3 to 5 Pa were developed when a closed conference room was occupied by 21 cigarette smokers or nine cigar smokers (Harke, 1970; Russell, Cole and Brown, 1973). Given a similar occupancy but moderate ventilation, the concentration of CO reached only 1 Pa (Harke, 1970), and readings were even lower when the room occupants were pipe smokers. Nevertheless, ventilation of public buildings is not always adequate, and CO concentrations of up to 3.7 Pa have been traced to the accumulation of cigarette smoke (Sebben, Pimm and Shephard, 1977).

5. EXPOSURE

5.1 Blood Carboxyhaemoglobin Levels in the General Population

Peak CO exposures as determined by physical instrumentation may have biological significance. However, CO is emitted intermittently in widely varying amounts by multiple point sources, all of which are moving. For this reason it is impossible to make any precise prediction of cumulative exposure as a person moves around a city. The relative stability of blood carboxyhaemoglobin (COHb) provides a biological method of integrating exposure, at least in a nonsmoker (Stewart et al., 1973a). Data are indicative of cumulative exposure for several hours, although COHb levels can still vary from day to day. Results are usually expressed as a saturation of the circulating haemoglobin (per cent). Gettler and Mattice (1933) made the first blood COHb determinations. Their values of 1.8 ± 1.2% for eighteen residents of New York City and 1.2 ± 1.0% for twelve "country dwellers" were "nowhere as low as... expected". They were unaware of endogenous CO production, stating that "the ideal normal individual should have no carbon monoxide in his blood" (Gettler and Mattice, 1933). A strong association was found between high COHb levels and smoking. Hanson and Hastings (1933) confirmed this conclusion, as have numerous other subsequent studies (Curphey, Hood and Perkins, 1965; Goldsmith and Landaw, 1968; Gothe et al., 1969; Longo, 1970; McIlvaine, Nelson and Bartlett, 1969; Ringold et al., 1962; Rode and Shephard, 1971; Stewart et al., 1973a; Wright and Shephard, 1978a).

Geographical location influences the COHb level of urban dwellers (Gettler and Mattice, 1933). High automobile densities are associated with high COHb saturations (Rode and Shephard, 1971; Rode and Shephard, 1973; Stewart et al., 1973a; Wright, Randell and Shephard, 1973). In Chicago and Los Angeles, three quarters of nonsmoking blood donors had COHb saturations greater than 1.5%, while in Milwaukee only 26% exceeded this figure. Values were even lower in small urban areas; in Vermont and New Hampshire only 18% of the people tested had COHb levels above 1.5% saturation (Stewart et al., 1973a). Kahn et al., (1974) concluded that ambient CO added little to the effects of smoking and occupation. In contrast, 17% of urban nonsmokers living near London, Ontario had COHb levels above 1.0% saturation (Wright and Shephard, 1978b). COHb levels for male nonsmokers were almost twice as high as those for female nonsmokers (De Bruin, 1967; Rode and Shephard, 1971). The probable reason is that the men were working in, or driving through a polluted area and women were not (Wright, 1976).

The mean COHb level for nonsmoking mothers can vary from 0.4 to 2.6% saturation, with reported mean foetal COHb levels of 0.7 to 2.5% saturation (Longo, 1970). For

any given level of exposure, COHb levels may be greater in the foetus than in the mother (Longo and Hill, 1970). Normal COHb levels for pregnant women are also elevated in comparison to other nonsmokers, in part as a result of the approximate doubling of endogenous CO production ($0.9 mL \cdot hour^{-1}$) due to such factors as an increase in the red cell mass, endogenous CO production in the foetus and increased haeme catabolism associated with high plasma progesterone levels (Delivoria-Papadopoulos, 1973; Delivoria-Papadopoulos, Coburn and Forster, 1974).

5.2 Blood Carboxyhaemoglobin Levels in Smokers

Smoking habits have a profound effect upon COHb levels, and (through adaptation to CO exposure) a smoker may have a greater tolerance of ambient CO than a nonsmoker. Unfortunately, many experiments fail to distinguish smokers from nonsmokers; this usually requires careful measurement of blood COHb, since 10 to 30% of smokers give misleading information on their smoking habits.

In two presumably unrefereed letters to a medical journal (Hickey, Clelland and Boyce, 1973; Hickey et al., 1974) the suggestion was recently made that the increased COHb levels of cigarette smokers were constitutionally determined. It would be incredible if constitution had a major impact upon the COHb levels seen with a given CO exposure. Nevertheless, the type and amount of tobacco usage are influenced somewhat by the individual's constitution, and genetic factors may also modify haemoglobin structure and thus the firmness of CO binding.

Absorption of CO occurs relatively slowly across the alveolar membrane, and relatively little can be taken through the lingual mucosa. On the other hand, people who smoke tobacco absorb a substantial proportion of the CO produced, even if they say that they do not inhale (Wald and Smith, 1974). Dudley (1888) noted that the CO from tobacco smoke that entered the lungs diffused into the blood stream. Amerson (1907) added that smoke from cigars and pipes was so "strong" that it "could not" be inhaled. Hartridge (1920) used the reversion spectroscope (Hartridge, 1912a) to demonstrate the presence of COHb in the blood of habitual smokers, although his methodology was not sensitive enough to yield consistent results. Dixon (1921) commented that the blood of a "cigarette inhaler" could contain up to 5% COHb. Baumberger (1923) compared the CO content of inhaled smoke to smoke puffed but not inhaled; he calculated that on the average, 61% of inhaled CO was retained in the lungs, in agreement with the 56% retention obtained by Haldane (1895b) for air/CO mixtures; more recent figures of 53% have been established by pulmonary function laboratories (Comroe et al., 1970; Shephard, 1958) and 54% has been cited for the absorption of CO from cigarette smoke (Dalhamn,

Edfors and Rylander, 1968). The results of Bokhoven and Niessen (1961) (82 to 87% of inhaled CO absorbed) are inconsistent with those of the other studies. However, lack of standardization of depth and length of inhalation could account for the discrepancy. Dalhamn et al., (1968) have estimated that 3% of mainstream CO is retained in the mouth.

There is good agreement regarding the average level of COHb observed in smokers, reported values including 4.7 ± 1.7% staturation in longshoremen just before commencing work (Goldsmith and Landaw, 1968), 3.5 ± 1.2% in Swedish police officers in Stockholm (Göthe et al., 1969), 5.3 ± 1.3% in blood donors smoking between one half and 2 packs of cigarettes per day (Stewart et al., 1973a), 4.7 ± 0.8% in police officers (Wright and Shephard, 1978a) and 4.9 ± 2.0% in male residents of London, Ontario (Wright and Shephard, 1978b). Higher levels (7.6 ± 2.3% saturation) were observed in heavily smoking males reporting to a smoking withdrawal centre (Delarue, 1973; Rode, Ross and Shephard, 1972). All of the above studies plus those of Buchwald (1969a), Curphey et al., (1965) and Ringold et al., (1962) have found COHb levels in excess of 7% for those who smoke between 1 1/2 and 2 packs of cigarettes per day. Those who smoke one half to 1 pack per day average between 3% and 4% saturation, as do those who smoke cigars and pipes. Since the CO burden from smoking cigarettes is not completely eliminated in 24 hours (Rode and Shephard, 1971), the COHb levels of subjects who did not smoke on the day of testing falls towards, but does not reach, the level observed in nonsmokers.

Different tobaccos yield smoke of differing composition (Hoffman and Wynder, 1972; Munro, 1964; Osborne et al., 1956). Russell et al., (1973) found a greater increase in blood COHb levels after smoking a "non-mild" compared to an "extra-mild" filter-tipped cigarette. They therefore proposed that the CO yield of cigarettes should be published together with their tar and nicotine content. Inter-subject differences in COHb levels are large (from 2.2% to 21.8%) suggesting the influence of additional variables, possibly including pulmonary function status (Cohen et al., 1971b).

Controversy has arisen regarding the generality of Russell et al.,'s (1973a) results, since his subjects all smoked at the same controlled rate (Ashton and Watson, 1970). Ashton and Telford (1973) suggested that subjects could unconsciously alter their puffing rate to obtain a given dose of nicotine, and might thus obtain more CO from low than from high nicotine cigarettes. Russel et al., (1973) confirmed that regular smokers "regulated" nicotine intake. A "safer" cigarette might thus be one with a relatively high nicotine content but a low tar and CO yield. However, Wright et al., (1974) observed that for

occasional smokers there was a greater increase of blood COHb with high than with low-nicotine cigarettes. Therefore the "safer" cigarette for social smokers is one low in tar and very low in nicotine. The results of both Russell et al., (1973a) and Wright et al., (1974) suggest that the female response to cigarette smoking is different from that of the male. Cigarette smokers have been advised to change to a pipe or cigars if they are unable to stop smoking. Unfortunately, those who change from cigarettes often continue to inhale (Castleden and Cole, 1973).

5.3 Blood Carboxyhaemoglobin Levels in Occupationally Exposed Populations

With a few notable exceptions, the COHb levels reached by occupationally exposed non-smokers are lower than those found in a heavy smoker without occupational risk.

Problems arise most frequently when CO is part of the finished industrial product. There may be leakage of CO, inadequate installation of equipment, or deficient ventilation (Grut, 1949). The blast furnace smelting of iron ore usually produces about six tons of gas (partial pressure of CO 26 kPa) for every ton of iron produced (Davies et al., 1965). Thus, even under "normal" working conditions the COHb levels of nonsmoking blast furnace personnel reach 2.3% to 14.9% saturation (Davies et al., 1965; Farmer and Crittenden, 1932; Jones and Walters, 1962). Grut (1949) lists many other working processes which produce high levels of CO; casting, welding, drying or preheating, boiler cleaning, chimney sweeping and transport of hot coke or slag. Stewart et al., (1973b) found COHb concentrations of greater than 2% in occupational groups involved with vehicles, metal processing, chemical processing, stone and glass processing, printing, welding, electrical assembly and repair work and certain types of graphic artwork.

Occupational exposure to CO is also associated with inhalation of vehicle exhaust fumes. One early study found COHb levels of 5 to 13% in policemen patrolling the most congested mercantile districts of Philadelphia (Wilson et al., 1926). Subsequent studies on nonsmoking police officers (De Bruin, 1967; Göthe et al., 1969; Moureu, 1964; Wright and Shephard, 1978a) and drivers of cabs and delivery vans (De Bruin, 1967; Jones, Commins and Cernik, 1972) have not found COHb levels higher than 5% saturation; indeed, the observed values have generally been quite low (2.3 ± 0.4% COHb), with only small increases over the working shift (± 0.3% COHb), suggesting that such workers may not be close to traffic as frequently postulated (Wright and Shephard, 1978a). Vehicle inspectors are one group that spend their working hours close to idling cars. Hofreuter et al., (1962) compared the mean COHb levels of nonsmoking and smoking vehicle inspectors and found that, after work, the two groups were indistinguishable (saturations of 3.4% and 3.8% respectively). Cohen et al., (1971a) observed that at the end of their shift, the COHb levels for nonsmoking and smoking U.S. border inspectors had increased

significantly from the pre-work levels of 1.5% and 4.8% saturation to 3.6% and 6.4% saturations respectively. Increases of COHb are greater in individuals controlling vehicles indoors, as in parking garages (Buchwald, 1969a; Ramsey, 1967), ship cargo holds (Breysse and Bovée, 1969; Gibbs et al., 1973), box cars (Hall et al., 1957), trailers (Linch and Pfaff, 1971) and confined warehouse areas (Bloomfield, 1957; Hall et al., 1957; Linch and Plaff, 1971). As in garages undertaking vehicle repairs (Bloomfield and Isbell, 1928; Buchwald, 1969b; Ciampolini, 1933; Henderson and Haggard, 1923; Katz and Frevert, 1928), inadequate ventilation and a limited cubic capacity are the principal causes of CO accumulation. These principles also apply to ice arenas where resurfacing can expose the operator, the players and the public to CO concentrations in excess of 5 Pa (D.E. Anderson, 1971; Johnson et al., 1975).

6. UPTAKE, METABOLISM, DISTRIBUTION AND ELIMINATION

6.1 Cellular Reactions of Carbon Monoxide

6.1.1. Haemoglobin

Carbon monoxide binds to protohaeme, a ferrous ion complex of protoporphyrin IX in the haemoglobin molecule; the site is the same as for the reaction with oxygen, but the affinity of carbon monoxide for the pigment is much greater (Antonini, 1967; Perutz, 1970; Roughton, 1964; 1970; Rodkey et al., 1974). The two haemoglobin dissociation curves can be virtually superimposed upon each other if allowance is made for respective affinities (Douglas, Haldane, and Haldane, 1912; Joels and Pugh, 1958) in accordance with Haldane's law:

$$\frac{(HbCO)}{(HbO_2} = M \frac{P_{CO}}{P_{O_2}}$$

where HbCO and $HbCO_2$ are the amounts of carbon monoxide and oxygen bound to haemoglobin, P_{CO} and P_{O_2} are the respective partial pressures, and M is the affinity ratio.

Both the reactions of oxygen with haemoglobin (Adair, 1925) and the analogous reactions for carbon monoxide (Holland, 1969a,b; Kernohan, 1961) can be represented by four consecutive reactions of the type:

$$Hb_4 + O_2 \underset{K_1}{\overset{K'_3}{\rightleftharpoons}} Hb_4O_2$$

$$Hb_4O_2 + O_2 \underset{K_2}{\overset{K'_2}{\rightleftharpoons}} Hb_4O_4$$

$$Hb_4O_4 + O_2 \underset{K_3}{\overset{K'_3}{\rightleftharpoons}} Hb_4O_6$$

$$Hb_4O_6 + O_2 \underset{K_4}{\overset{K'_4}{\rightleftharpoons}} Hb_4O_8$$

The equilibrium constant M depends on the magnitude of the various reaction constants, particularly those for the fourth reaction

$$M = \frac{1'_4 \cdot k_4}{K'_4 \cdot 1_4}$$

where $1'_4$ and 1_4 are the corresponding fourth stage reaction constants for the binding of carbon monoxide. The association velocity constants for CO are only about $1/5^{th}$ to $1/6^{th}$ of those for oxygen, but the dissociation constants are $1/1800^{th}$ of those for the oxygen reaction (Forster, 1969a).

When a mixture of oxygen and carbon monoxide is present, the net effect on the oxygen dissociation curve of haemoglobin is leftward displacement, with a more hyperbolic format similar to the myoglobin curve; there is a reduction of tissue oxygen pressures for a given oxygen content (Haldane and Priestley, 1935; Roughton and Darling, 1944), the P_{50} value dropping from 3.56 to 3.09 kPa (Mulhausen et al., 1968). This is due to an elimination of low-concentration binding sites from the haemoglobin dissociation curve, rather than any more fundamental change in the haemoglobin molecule. Patients with sickle-cell anaemia seem particularly vulnerable to displacement of the oxygen dissociation curve when exposed to CO (Cameron et al., 1972).

The impairment of oxygen transport for a given CO-induced change of venous oxygen saturation is much greater than would be anticipated for an equivalent anaemia, and there have been suggestions that the resultant tissue hypoxia is sufficient to cause the vascular lesions found in many smokers (Åstrup, Kjeldsen and Wanstrup, 1967). This plainly, could be important in setting air quality criteria, but the original experiments were based on severe CO exposures (30% COHb). Further long-term animal experiments have shown ECG abnormalities, cardiac hypertrophy and/or dilatation, muscle degeneration and necrosis, sub-endothelial infiltration with cells and lipid material (Ehrich et al., 1944; Kjeldsen et al., 1974; Lindenberg et al., 1961; Lewey and Drabkin, 1944; Penney et al., 1974; Stender et al., 1977; Thomsen, 1974; Thomsen and Kjeldsen, 1974; Tumasonis and Baker, 1972; Webster et al., 1968). However, with one possible exception (Lindenberg et al., 1961) animals have been exposed to very high concentrations of CO (partial pressure > 10 Pa) for some months, resultant COHb readings being in the range 10-20%. The findings have possible implications for cigarette smokers but are irrelevant for air quality criteria.

Unlike the usual situation at altitude, some authors see no evidence of adaptation to CO-induced hypoxia through an alteration in the oxygen-binding properties of haemoglobin (Mulhause, Åstrup and Mellemgaard, 1968). Others find CO-induced changes of 2,3-diphosphoglycerate.

Some authors have found a variation of M with pH (Allen and Root, 1955a; Joels and Pugh, 1958), values rising from about 180 at a plasma pH of 7.15 to a maximum of 230 at pH 7.35, and thereafter falling to 140 at pH 7.70. Others find no change with pH (Douglas et al., 1912; Rodkey, O'Neal and Collison, 1969), oxygen pressure (Douglas et al., 1912) or 2,3- DPG levels (Benesch and Benesch, 1967), although there is agreement that the affinity ratio is modified by temperature and exposure to light (Gibson and Ainsworth, 1957). It also varies over differing segments of the oxygen dissociation curve (Roughton, 1970).

6.1.2 Myoglobin

The affinity of carbon monoxide for intracellular compounds is usually given in terms of the Warburg partition coefficient K, which describes the ratio of carbon monoxide to oxygen required for 50% saturation with carbon monoxide; in essence, it is the reciprocal of M.

The Warburg coefficient for myoglobin is in the range of 0.05 (Millikan, 1939) to 0.025 (Coburn, 1970; Coburn et al., 1973; Luomanmaki, 1966; Rossi-Fanelli and Antonini, 1958). The rise of carboxymyoglobin levels lags behind that of carboxyhaemoglobin (Godin and Shephard, 1972). Under normal steady state conditions blood and muscle pigment saturations become equalized (Coburn et al., 1973), but hypoxia can increase the myoglobin/haemoglobin carbon monoxide saturation ratio from 1.0 to around 3.0, both in cardiac (Coburn et al., 1973) and skeletal (Coburn and Mayers, 1971) muscle. Thus, as the arterial oxygen pressure falls, CO is displaced from blood to muscle (Coburn et al., 1973; Luomanmaki, 1966). The oxygen pressure is usually a little lower in cardiac tissue (0.5-0.8 Pa) than in skeletal muscle (0.8-1.1 Pa), and in the heart a 10% blood COHb may lead to a 30% CO-myoglobin saturation. The functional consequences of myoglobin-CO saturation are uncertain, although it is known that myoglobin provides a temporary oxygen store for brief bursts of interval work, and also facilitates the diffusion of oxygen within the muscle fibres (Wilks, 1963).

6.1.3 Cytochrome Pigments

It has been argued that combination of carbon monoxide with the various cytochrome pigments is of little significance at usually encountered CO pressures (Root, 1965). This is probably true of equilibrium values, but if a bolus of CO is administered, the finite rate of reaction with haemoglobin may temporarily allow an escape of CO to tissue pigments (Goldbaum, 1977). Some of the animal experiments showing such an effect have used CO concentrations up to 10 kPa.

The final status of the tissue pigments depends not only on partial pressures of CO, but also upon the intracellular partial pressure of oxygen. Some work based on carbon monoxide binding to myoglobin and the use of polarographic microelectrodes indicates an intracellular oxygen pressure of 0.53 to 0.80 kPa (Coburn et al., 1973; Kessler et al., 1973; Whalen, 1971), but at some points within the cell pressures may be lower (Shephard, 1977), particularly in the presence of carboxyhaemoglobin. Measurements of peritoneal CO pressures in the rabbit have shown values 42 to 69% of those in alveolar gas (Göthert et al., 1970).

The Warburg coefficient for cytochrome a_3 varies from 2-30 (Ball, Strittmatter and Cooper, 1951; Coburn, 1977). Early workers estimated that the CO pressure needed to produce 50% saturation of "cytochrome oxidase" (a mixture of cytochrome a and cytochrome a_3) was 21 to 29 Pa (Gibson and Greenwood, 1964; Wald and Smith, 1974). Interpretation of data is complicated by the fact that most measurements were made at 25°C rather than 37°C. The computed tissue P_{CO} with 5% carboxyhaemoglobin is about 0.27 Pa, so that in the worst case (K for cytochrome a_3 = 2), the mitochondrial oxygen pressure would need to drop to 0.13 Pa for 50% binding (Longo, 1977). In essence, CO binds only with the reduced form of cytochrome a_3. A further rise of carboxyhaemoglobin to 10% or severe tissue hypoxia (<0.13 Pa) could make the binding of physiological significance, although oxygen consumption is unaffected by 50% inhibition of this enzyme (Forster, 1969a).

The Warburg coefficient for cytochrome P-450 varies from 0.2 to 5.0; the system seems sensitive to carbon monoxide when electron transport is rapid, but with slow electron transport it becomes almost refractory to CO (Estabrook, Franklin and Hildebrandt, 1970). Practical evidence of impaired function includes a decreased hepatic metabolism of 3-OH-benzo-alpha-pyrene in rats exposed to 6 Pa of CO (Rondia, 1970) and a decreased catabolism of haemoglobin-haptoglobin in dogs with a 10 to 12% carboxyhaemoglobin level (Coburn and Kane, 1968). However, it is still unclear how far tissues can compensate for the poisoning of redox enzymes by an increase of perfusion; this seems probable

under resting conditions, but might not be possible during vigorous exercise. One argument against any major cellular effect is the fall of tissue oxygen pressure during CO poisoning (Weiss and Cohen, 1974; Zorn, 1972).

Carbon monoxide could theoretically interact with the reduced form of other haeme protein enzymes, including catalase and peroxidase. However, the reaction is extremely unlikely to occur in practice, since these compounds are not normally present in a reduced form in the body.

6.2 Endogenous Production of Carboxyhaemoglobin

Under normal circumstances, the urban nonsmoker has a blood carboxyhaemoglobin level of ~ 1% (Coburn, Forster and Kane, 1965; Rode and Shephard, 1971). About a half of this burden is attributable to the endogenous production of CO (Sjöstrand, 1949 and 1951) which has been estimated at 0.41 $mL \cdot h^{-1}$ (Coburn, Blakemore and Forster, 1963; Luomanmaki, 1966), or 5-10 x 10^{-3} $mL \cdot kg^{-1} h^{-1}$ (Delivoria-Papadopoulos, Coburn and Forster, 1974; Lynch and Moede, 1972). Some three quarters of the endogenous CO is derived from the alpha methene carbon atom of heme (Coburn et al., 1967) during erythrocyte breakdown (Coburn, Williams and Forster, 1964; Lundwig and Blakemore, 1957; Sjöstrand, 1952a,b). The process is increased by fasting (Mercke et al., 1975), administration of drugs such as phenobarbital and diphenylhydantoin (Coburn, 1970), pregnancy (Longo et al., 1967), elevation of plasma progesterone (Delivoria-Papadopoulos et al., 1974), simulated saturation dives (Rodkey et al., 1974) and haemolytic disease (Coburn et al., 1966; Engel, Rodkey and Krill, 1971; Sjöstrand, 1949).

A further endogenous source of CO is the catabolism of hepatic haeme containing enzymes (Coburn, 1973). One possible industrial source is exposure to methylene chloride; this is absorbed and oxidized to CO within the body (Ratney, Wegman and Elkins, 1974). The turnover of myoglobin is slow, and for this reason it probably contributes little to endogenous CO production (Forster, 1969b).

6.3 Uptake and Distribution

Almost all of the body CO is stored in combination with haeme pigments (Coburn, 1967), some 80% being bound to haemoglobin, 15% to myoglobin, and up to 5% to other haeme compounds (particularly in the liver); as noted previously, hypoxia encourages CO storage in myoglobin at the expense of haemoglobin (Coburn and Mayers, 1971).

The rate of buildup of blood carboxyhaemoglobin is relatively slow, and since high CO pressures are usually encountered only for a few minutes (for example, when driving through a tunnel), the speed of absorption has an important bearing upon acceptable

concentrations. Unfortunately, available data are based on relatively small groups of subjects, using poorly controlled techniques, so the end-results differ substantially between investigators. Most studies have been conducted under resting conditions, and there is no information about vigorous exercise (when CO uptake proceeds the most rapidly).

It is well recognized that the buildup of COHb depends largely on the volume of air breathed relative to body mass (and thus blood volume) (Haldane, 1895a; Henderson, and Haggard, 1921). Under resting conditions, only about a half of the respired dose is retained in the body (Forbes, Sargent and Roughton, 1945; Haldane, 1895a) owing to the effects of dead space and back-pressure at the alveolar-capillary interface. During light work, the initial retention remains around 50%, but in heavier work (~ 100 Watts, heart rate 135 beats·min^{-1}) only 40% of the CO is retained (Forbes, 1970; Lilienthal and Pine, 1946). The rate of uptake is also reduced by a rising back-pressure in the pulmonary capillaries when subjects have absorbed more than a third of the equilibrium quantity (Forbes et al., 1945; Haldane, 1895a). Finally, in older subjects it may be necessary to allow for a decline of pulmonary diffusing capacity due to emphysema (Bates, 1952) or other forms of chronic obstructive lung disease (Ramsey, 1972). As a general guideline, the halftime for uptake in a healthy adult performing light activity is about 2 hours (Brody and Coburn , 1970).

6.4 Elimination

Carbon monoxide is eliminated almost entirely via the lungs, less than 1% of the gas being oxidized within the body (Fenn and Cobb, 1932; Luomanmaki, 1966; Roughton and Root, 1945).

Most authors have assumed a single exponential curve for carbon monoxide elimination. Typical halftimes for resting conditions have been 3 to 4 hours breathing air, and about 1-hour breathing oxygen (Bartlett, 1968; Pace, Stajman and Walker, 1950; Roughton and Root, 1945), with somewhat faster rates at very high carboxyhaemoglobin concentrations (Haldane, 1895a; Henderson et al., 1921) and slower rates at very low concentrations (Peterson and Stewart, 1970).

Rode et al., (1972) pointed out two problems with most reports - (i) halftimes were calculated without reference to the normal urban background of ~ 1% carboxy-haemoglobin, and (ii) similar rates of CO elimination were assumed for men and women. Their analysis of data for a smoking withdrawal clinic indicated halftimes of 3.7 hours for men and 2.5 hours for women. The failure to allow for the influence of background CO probably explains longer, more variable and concentration dependent halftimes

reported by other investigators (Coburn et al., 1965; Mercke et al., 1975; Myhre, 1974). However, there remains a need for further study, particularly at low COHb levels. Other potential variables include the age and health of the subjects, possible redistribution of carbon monoxide into poorly perfused vascular compartments such as the spleen and bone marrow and allowance for reactions with extravascular pigments (Godin and Shephard, 1972; Killick and Marchant, 1959; Roughton and Root, 1945; Tobias et al., 1945). Roughton and Root (1945) commented that 60 to 70% of the gas leaving the blood in the first hour was expired, while Godin and Shephard (1972), Wagner, Horvath and Dahms (1975) and Myhre (1974) have all noted a biphasic CO elimination curve. Presumably, much depends on the speed of CO administration. A physiological analogue, based on the probable distribution of the cardiac output and the sizes of the various tissue compartments (Godin and Shephard, 1972) suggested that carboxymyoglobin concentrations rose steadily during 6 minutes of exposure to a high concentration of CO, while there was an "over-shoot" of COHb% in the pulmonary capillary blood and the rapidly circulating blood volume. During the first 5 minutes of the recovery period, equilibrium between the various vascular compartments was completed, but carbon monoxide continued to penetrate into the myoglobin for up to one hour.

While most authors continue to advocate exponential clearance models, Wagner et al., (1975) found that their data for 15 to 90 min. post-exposure were satisfied by a linear equation; during this period, clearance was determined by the affinity constants for haemoglobin and myoglobin, rather than minute ventilation or cardiac output.

Although the respiratory centres of a poisoned subject are already depressed by hypoxia (Donald and Paton, 1955), clearance of carbon monoxide apparently proceeds most rapidly when breathing a mixture of 5% carbon dioxide in oxygen (Henderson and Haggard, 1921; Killick, 1936; Medical Research Council, 1958, Malorny et al., 1962). No additional advantage is gained from the use of a 7% CO_2 mixture (Norman and Ledingham, 1967), but the halftime of elimination can be reduced to approximately 23 minutes at an oxygen pressure of 3 atmospheres (Kindwall, 1977; Pace et al., 1950).

6.5 Models

Various models have been developed to predict the uptake and release of carbon monoxide from the body.

Forbes et al., (1945) proposed the empirical equation:

$$\text{Rate of CO uptake} = KP_{CO} \frac{(COHb_{\infty} - COHb_{T})}{(COHb_{\infty} - COHb_{0})}$$

with K being a constant proportional to the intensity of physical activity, P_{CO} the partial pressure of CO in inspired air, and COHb the concentration of carboxyhaemoglobin initially (o), at any given time (τ), and at equilibrium (∞) as indicated by the subscripts. The increase of COHb% was given by the formula:

$$\Delta \text{ COHb\%} = K' (\% \text{ CO})\tau$$

where K' was a constant of 3 to 11 (increasing nonlinearly with ventilation and heart rate) and τ was the duration of exposure in minutes. The base data involved 6 hr. exposures to 100 to 20 000 ppm (10 Pa - 2 kPa). Commonly encountered urban concentrations were thus not tested. Assuming an initial blood COHb content of less than 5%, the equation gave valid results to a ΔCOHb of 7% at 10 Pa and 30% at 100 Pa.

Larsen and Burke (1969) suggested the same equation, using K values of 3 for resting conditions, 8 for light to moderate work (ventilation 18 L/min) and 16.7 for heavy work.

Lilienthal and Pine (1946) also proposed an analogous equation:

$$\Delta \text{ COHb\%} = 0.05 \dot{V}_E (P_{CO})\tau$$

where $\dot{V}_E$ was the respiratory minute volume in $L \cdot min^{-1}$, and P_{CO} was measured in Torr. Expressing CO as percent, this would yield K values of 2.28 and 11.4 respectively with $\dot{V}_E$ equal to 6 and 30 $L \cdot min^{-1}$ respectively. Their base data covered rest and light activity at CO pressures of 5 Pa to 275 Pa.

Pace et al., (1946) further developed this type of equation, adding a term for blood volume:

$$\Delta \text{ COHb\%} = \frac{100 \dot{V}_E (\% \text{ CO})\tau}{46.5 \text{ (Blood volume, litres)}}$$

Their formula was considered valid for partial pressures of 10 to 200 Pa_{CO}, from the onset of exposure until blood COHb levels reached one third of equilibrium values. The standard deviation of the estimate was 2.3% COHb. Results were identical with the equation of Forbes et al., (1945) only if blood volumes of 4.3, 4.1, 4.9 and 5.9 litres were assumed for the four work loads.

Goldsmith, Terzaghi and Hackney (1963) were the first to attempt a dynamic representation of CO uptake and release. Their equations were:

$$\text{Uptake } (\Delta \text{ COHb\%})t = (\text{COHb\%}_\infty - \text{COHb\%}_o)\ (1 - e^{-0.004t})$$

$$\text{Release } (\Delta \text{ COHb\%})t = (\text{COHb\%}_o - \text{COHb\%}_\infty)\ (1 - e^{-0.0033t})$$

The uptake constant of 0.004 was derived from a graphic analysis of the data of Forbes et al., (1945), while the excretion constant of 0.0033 corresponded to a halftime of elimination of 3.5 hr. The equations of Goldsmith et al., (1963) are widely accepted in the U.S. The base-data covers relatively high CO concentrations (10 Pa - 2 kPa) at ventilations of 6 to 30 $L \cdot min^{-1}$. Presumably, only the resting data of Forbes et al., - was used. The resultant equations give a good description of long-term changes of COHb%, but are much less satisfactory when applied to short-term transients.

Hanks and Farquhar (1969 - cited in WHO, 1979) developed the formula:

$$\Delta \text{ COHb\%} = 1470 \text{ (CO\%)} (1 - e^{-0.00289t})$$

Putting t = 480 min, this would be equivalent to the formula of Forbes et al., (1945) with a K of 2.3. For the shorter period of 60 min, K would rise to 3.9.

Chovin (1974 - cited in WHO 1979) proposed modifying this formula to allow for varying degrees of physical activity:

$$\Delta \text{ COHb\%} = 1470 \text{ (CO\%)} (1 - e^{-Kt/0.147})$$

where K = 0.025 at rest, increasing to K = 0.065 in heavy physical work, and t = time in hours.

Coburn et al., (1965) developed a more sophisticated formula that introduced many pertinent physiological variables, including the pulmonary capillary oxygen pressure (P_{c,O_2}), the affinity ratio (M), the oxygen saturation (HbO_2%), the pulmonary diffusing capacity ($\dot{D}_L$), alveolar ventilation ($\dot{V}_A$), endogenous CO production ($\dot{V}_{CO}$), blood volume (V_b), and total inspired gas pressure (P_I). The basic differential equation was:

$$\frac{\partial [CO]}{\partial \tau} = \dot{V}_{CO} - \frac{[HbCO]}{[HbO_2]} \cdot \frac{\bar{P}_{c,O_2}}{M} \left[\frac{1}{\frac{1}{\dot{D}_{L_{O_2}}} + \frac{P_I^{-47}}{\dot{V}_A}} \right] \cdot \left[\frac{P_{I,CO}}{\frac{1}{\dot{D}_{L_{O_2}}} + \frac{P_I^{-47}}{\dot{V}_A}} \right]$$

whence

$$\frac{A \ [COHb\%]_t - \dot{V}_{CO}B - P_{I,CO}}{A \ [COHb\%]_o - \dot{V}_{CO}B - P_{I,CO}} = \exp \frac{-tA}{M \cdot Vb \cdot B}$$

where $A = \frac{P_{\bar{c},O_2}}{[M\,HbO_{2\%}]}$ and $B = \left[\frac{1}{\dot{D}_L} + \frac{P_I - 47}{\dot{V}_A}\right]$

Since HbO_2 depends upon HbCO in a complex way, the ratio $\frac{HbCO}{HbO_2}$ is difficult to determine precisely; one possibility is an iterative computer procedure.[2] Like the model of Goldsmith et al., (1963), a further problem with predictions based upon this formula is the unduly slow indicated response to changes in atmospheric CO pressures; the predicted halftime for the elimination of CO under typical resting conditions is 252 min. At equilibrium, the exponential term becomes zero, and total blood COHb% is given by the sum of endogenous and exogenous terms:

$$[\,COHb\%\,] = \frac{\dot{V}_{CO}\,M\,[\,HbO_2\%\,]}{P_{\bar{c},O_2}}\left[\frac{1}{\dot{D}_L} + \frac{P_I - P_{H_2O}}{\dot{V}_A}\right] + \frac{P_{I,CO}\,M\,[\,HbO_2\%\,]}{P_{\bar{c},O_2}}$$

Despite these problems, many observers consider the model of Coburn et al., (1965) as the best representation of the facts. Peterson and Stewart (1970) used an empirical logarithmic format, as follows:

$$\log\,[\,\Delta\,COHb\%\,] = 0.857\,\log\,[\,C_{I,CO},\,ppm\,] + 0.629\,\log\,[\,t,\,min\,] - 2.295$$

Rearranging in the same format as earlier equations, it reads:

$$\Delta\,COHb\% = 0.0051\,[\,C_{I,CO},\,ppm\,]^{0.858}\,[\,t\,]^{0.629}$$

The subjects for this experiment (18 healthy graduate students) were exposed to much more realistic CO pressures (0.1 - 100 Pa) for periods of 30 min to 24 hrs. Unfortunately, only sedentary conditions were tested, and the equation applies to constant CO pressures rather than the sharp ambient peaks encountered for example in urban driving.

Finding a rather long estimated halftime for CO elimination (128 - 409 min, average 320 min), Peterson and Stewart modified their equation to take account of this factor:

$$\Delta\,|\,COHb\%\left[= \frac{CO^{0.858}\,(ppm)\cdot t^{0.63}\,(min)}{197}\right] 10^{-0.00094t}$$

The standard error of the revised equation (1.18% COHb) was slightly larger than that for the formula of Coburn et al., (1965) (0.97% COHb). An alternative formula (Peterson and Stewart, 1972) was proposed for brief exposures to very high carbon monoxide concentrations.

log (Δ COHb% per litre of air breathed) = 1.036 log ($C_{I,CO}$ppm) - 4.4793.

This formula would imply a ΔCOHb of 14% over 380 minutes, given a CO pressure of 10 Pa (100 ppm) and a ventilation of about 7.1 L·min^{-1}.

Finally, Ott and Mage (1978, cited in WHO 1979) proposed a differential equation that would allow for the ever-changing characteristics of urban CO exposure:

$$\tau \frac{\partial [\text{HbCO\%}]}{\partial t} + [\text{HbCO\%}] - \beta = \alpha [\text{CO, ppm}]$$

In this expression τ = 2.49h, α is 0.15 and β is the endogenous carboxyhaemoglobin, assumed to be 0.5%. The equation is applicable to anticipated urban CO pressures (0-10 Pa, 0-100 ppm), and yields somewhat more accurate results than methods where CO pressures are averaged over longer periods.

The various equations unfortunately lead to substantially varying estimates of blood COHb% for a given CO exposure (Table 2 and Table 4).

Hill et al., (1977) have recently developed the Coburn equation for the exchange of CO between the mother and foetus. For the mother,

$$\frac{\partial [\text{HbCO}]}{} = \frac{100}{\text{Blood volume}_m} \left[\dot{V}_{CO_m} + \dot{D}_{L,CO} (P_{A,CO} - P_{c,CO}) - (\dot{D}_{P,CO} P_{\bar{m},CO} - P_{\bar{f},CO}) \right]$$

and for the foetus,

$$\frac{\partial [\text{HbCO}]}{\partial t} = \frac{100}{\text{Blood volume}_f} \left[\dot{V}_{CO_f} + \dot{D}_{P,CO} (P_{\bar{m},CO} - P_{\bar{f},CO}) \right]$$

Here, the subscripts m and f refer to maternal and foetal conditions, $\dot{V}_{CO}$ is endogenous production of CO, $\dot{D}_P$ is the diffusing capacity of the placenta, $P_{\bar{m},CO}$ and $P_{\bar{f},CO}$ are mean pressures in the maternal and placental capillaries, and other symbols are as previously defined.

7. HEALTH EFFECTS - STUDY DESIGN

7.1 Chamber Exposure

There is no fundamental reason why experimental exposures to carbon monoxide should not be carried out, using large military-type gas chambers where groups of men can be exposed simultaneously. However, for reasons of expense, exposures are often conducted on single subjects sitting in very small chambers (O'Donnell, Chikos and Theodore, 1971; O'Donnell et al., 1971; Theodore, O'Donnell and Back, 1971; Wright and Shephard, 1978c). Under such circumstances results could be complicated by sensory isolation (in uncontrolled experiments), or a possible interaction between carbon monoxide and sensory isolation (in supposedly controlled experiments).

The advantages of chamber exposure are (i) concentrations can mimic those in the urban environment, and (ii) the subject is not aware when exposure has commenced.

7.2 Rapid Rebreathing Exposure

Godin and Shephard (1972) developed a rapid rebreathing technique, whereby a known amount of pure CO (40-100 mL) was added to a 2-litre bag of oxygen. After two minutes of rebreathing, a relatively constant increment of COHb% was produced, ranging from 2.4% with 40 mL to 5.4% with 100 mL of CO. Control rebreathing bags filled with air and oxygen were prepared in a single or double-blind manner.

The advantages of this approach are (i) safety (it is impossible for the required dose of CO to be exceeded), and (ii) a sharply delineated onset of the increase in blood COHb%. The pattern of exposure is somewhat analogous to the smoking of one or more cigarettes. The main disadvantage is that carbon monoxide is usually undergoing redistribution between the various body compartments while its effects are being observed; therefore, initial blood concentrations exceed equilibrium values.

7.3 Epidemiological Studies

Much recent work has been based on the epidemiology of incidental industrial and urban exposures. While it can be argued that the ultimate proof of the toxicity of low doses of carbon monoxide lies in the demonstration of effects upon city dwellers, such research is beset by many pitfalls (Shephard, 1974). In many cities, CO concentrations are normally below the probable threshold for physiological and/or pathological responses. Available data refer to a limited sampling network, and are often unrepresentative of individual exposure patterns. Apparent correlations between temporal regional peaks of CO exposure and poor health may be traced to such associations as exposure to pollution and

cold weather, exposure to pollution and poor socioeconomic conditions, or exposure to pollution and cigarette smoking. Incidental exposure may even fail to show clear peaks, and it is then difficult to establish reference points for detection of a subsequent response. Fortunately, with many of the probable effects of carbon monoxide, difficulties due to a "lag-period" are less than for other pollutants (Shephard et al., 1960). Finally, for more than 40% of the adult population self-administration of carbon monoxide by cigarette smoking far exceeds incidental urban exposure (Rode et al., 1972).

7.4 Animal Models

Animal experiments have several important uses in the context of air quality control. In particular, doses of pollutant can be larger than in man, exposure can continue for a substantial portion of the life-span, and body tissues can subsequently be examined for pathological changes.

In the context of CO exposure, problems include species differences in the oxygen dissociation curve of haemoglobin, differences in the CO affinity of haemoglobin (Klimisch et al., 1975) and difficulties in detecting subtle changes of psychomotor performance in animals.

8. CARDIORESPIRATORY EFFECTS

A number of experiments investigating cardiorespiratory effects of CO have used "bolus" exposures, or have failed to separate smokers and nonsmokers. Moreover, the subjects have usually been healthy and sometimes well-trained young men. It appears that quite moderate increases of COHb influence the physiological response to sub-maximal and maximal exercise. Although relatively easily measured, such changes have little practical significance for the healthy adult, other than causing a minor decrement in athletic performance. ECG (electrocardiogram) changes and impairment of contractility have been demonstrated in animal experiments, but the doses of CO used have been very large. It is thus debatable whether the demonstration of such effects should influence air quality standards.

8.1 Heart Rate and Ventilation at Rest

Experiments on the cat have shown that substantial levels of carbon monoxide poisoning (COHb% 18-40%) lead to a two to fivefold increase of impulse traffic from the carotid chemoreceptors (Duke, Green and Neil, 1952; Mills and Edwards, 1968; Paintal, 1967). The response is observed despite an increase of arterial oxygen pressure, hypotension, or a direct effect of CO on cytochrome oxidase, and by exclusion it has thus been attributed to the onset of tissue hypoxia. Brain and muscle P_{O_2} decrease by 10.6 Pa during exposure to 8 Pa of CO (Weiss and Cohen, 1974).

Permutt and Farhi (1969) estimated that a 9% increase of COHb% would lower venous P_{O_2} by 0.53 to 0.80 kPa and more in tissues with a wide arterio-venous oxygen difference. Unfortunately, the precise arterio-venous oxygen difference for the carotid body is unknown; it is probably about 5 $mL \cdot L^{-1}$. On this basis, Comroe (1965) calculated that a 50% increase of COHb% would be needed to lower the end-capillary oxygen pressure from 11.7 to 10.6 kPa. The isocapnic ventilatory response of the carotid body over this range of oxygen pressures is 361 $mL \cdot min^{-1}$ per kPa. Thus in Comroe's calculation, ventilation would increase by 1.1 x 361 $mL \cdot min^{-1}$ (Loeschke, and Gertz, 1958), and a more modest 5% increase of COHb% should increase ventilation by a detectable 38 $mL \cdot min^{-1}$.

In fact, changes of heart rate and ventilation with exposure to mild doses of carbon monoxide have been small and equivocal (Horvath, Dahms and O'Hanlon, 1971; Klausen et al., 1968; Shephard, 1972; Weiss and Cohen, 1974). With severe CO poisoning, some authors have found hyperventilation, both in goats (Santiago and Edelman, 1976) and man (Leathart, 1962); this has been attributed to a tissue acidosis rather than chemoreceptor

stimulation, and has been advanced as an argument against provision of CO_2 mixtures for patients with CO poisoning (Leathart, 1962). Others (Chiodi et al., 1941) found no respiratory response to severe poisoning; presumably, in these experiments the respiratory centres were depressed by the hypoxia. A small (16%) increase of cardiac output has been reported in severe CO poisoning (Asmussen and Vinter-Paulsen, 1949).

8.2 Heart Rate and Ventilation with Sub-maximal Exercise

Asmussen and Chiodi (1941) and Apthorp et al., (1958) found that neither respiratory minute volume nor respiratory rate changed during steady state exercise, even at COHb levels in excess of 30% saturation. However, heart rate increased significantly in all subjects, a factor that can influence tolerance of sustained activity. Pitts and Pace (1947) reported that during mild exercise, the heart rate was unchanged at a COHb level of 6%, but increased at 13% saturation. Subsequent studies (Ekblom and Huot, 1972; Klausen et al., 1968; Pirnay et al., 1971; Vogel et al., 1972) have shown no significant change in the oxygen cost of activity. Cardiorespiratory responses are dependent on both the intensity of exercise and the % COHb. Generally, the higher the percentage of $\dot{V}_{O2\ max}$ that is required, the lower the COHb level needed to increase respiratory minute volume and heart rate. In some studies, confusion has arisen because the intensity of effort has been expressed as a percent of $\dot{V}_{O2\ (max)}$ before poisoning. Part of the effect may arise from chemoreceptor stimulation (as discussed above) and part from interference with oxygen transport to the working muscles (Calverley et al., 1979). The majority of reports have concerned high levels of COHb%. Chevalier et al., (1966) noted an increase of oxygen debt in smokers (3.95% COHb) relative to nonsmokers, but this may have reflected long-term vascular change, or a response to other constituents of cigarette smoke. Gliner et al., (1975) had their subjects work for a longer period than many authors (4 hr. at 35% of $\dot{V}_{O2\ max}$). The heart rate was increased by exposure to a CO pressure of 5 Pa; although the final COHb% reached surprisingly high levels (10.3% and 13.2 in nonsmokers and smokers respectively).

8.3 Maximal Performance

Changes of maximal performance can be detected with quite modest CO exposures. Further, the Δ COHb%/Δ $\dot{V}_{O2\ (max)}$ relationship seems to be approximately linear, with no evidence that the response is influenced by the pattern of CO exposure (high pressure/short time or low pressure/long time). The intercept for this relationship differs significantly from zero. Thus, in this respect there is no minimum threshold for a CO effect. Surprisingly, smokers seem less susceptible to a decrease of aerobic power.

The lowest CO pressure producing an effect (3 Pa) was recorded in a study of competitive swimming performance (Goldsmith, 1970). The CO was produced by traffic, so that other pollutants may have contributed to the observed loss of performance. Further, COHb% was not measured.

Heart rate, respiratory minute volume and respiratory rate during maximum exercise remain unchanged after exposure to CO (Ekblom and Huot, 1972; Maugh, 1972; Vogel et al., 1972), but there is a decline of maximal $\dot{V}_{O_2}$ approximately proportional to the increase of blood COHb (Vogel and Gleser, 1972). It is probable that COHb formation is the main reason for loss of aerobic power. Clark and Coburn (1975) have also postulated a role for intracellular responses to CO, but if this were true, "bolus" administration should produce more effect than a typical ambient exposure. Raven et al., (1974) and Horvath et al., (1975) have suggested that the decline of aerobic power becomes nonlinear at a COHb saturation of less than 6%. Nevertheless, the decrement of $\dot{V}_{O_2}$ observed at COHb levels below 4%, although not statistically significant with the small number of subjects used, was much as would be expected with a linear response to CO. Although the experiments were "double-blind" in design, the subjects identified correctly the experiments in which they had inhaled high concentrations of CO; under these conditions, the lower extremities felt heavy and the task seemed more difficult.

Other authors noted decrements of exercise endurance time (for example 38% at 7% COHb in the study of Ekblom and Hout, 1972) plus a decrease in capacity to perform physical work (Seppänen, 1977). Both Drinkwater et al., (1974) and Raven et al., (1974) found a shortening of working time at a CO pressure of 5 Pa, with a rise in COHb of 2.1% (to 2.8%) in nonsmokers and 2.6 to 3.2% (to 4.1-4.5%) in smokers.

9. EFFECTS ON THE CENTRAL NERVOUS SYSTEM

9.1 General Considerations

The possible effects of CO on the central nervous system (CNS) deserve careful discussion, since some responses have been claimed in healthy adults at COHb levels as low as 2.0 to 2.5%. This would be of possible significance in its own right (a detectable effect) and might also affect morbidity through an increased accident rate.

Investigation is hampered by (1) the obvious difficulty in conducting psychomotor tests on animals, (2) the lack of precision in psychomotor tests used in man, (3) prolonged learning schedules for many tests, (4) a substantial reserve of mental function which is normally untapped, (5) changes of cerebral arousal developing over the course of experiments, and (6) possible delayed adaptations to CO poisoning (such as cerebral vasodilatation).

Animal experiments suggest that even a 2% increase of COHb is sufficient to reduce tissue oxygen pressures within the brain (Zorn, 1972). It should be stressed that these findings indicate impaired oxygen delivery with unchanged tissue oxygen usage. In dogs, a compensatory increase of cerebral blood flow was not observed below a COHb saturation of 20% (Häggendal et al., 1966). The increased flow at higher doses of CO was insufficient to prevent a widening of the cerebral arterio-venous oxygen difference, but there was no evidence of cerebral hypoxia since jugular vein lactate concentrations were unaltered.

Many authors have found no significant effects of CO upon the human central nervous system (CNS), even at very high blood carboxyhaemoglobin levels. Forbes et al., (1937) reported no alteration of reaction time, binocular vision, and eye-hand coordination despite a COHb level of 30% saturation. Again, Stewart et al., (1970) found no change of hand and foot "reaction times", hand-steadiness, manual dexterity, visual acuity, depth perception and time estimation with COHb levels of 11% to 13%, while O'Donnell et al., (1971) detected no changes of critical fusion frequency, time estimation, and mental arithmetic ability with COHb levels up to 12.7%.

In contrast, McFarland et al., (1944) and Halperin et al., (1959) both noted changes of visual intensity discrimination at COHb levels of 3 to 5%. Likewise, Schulte (1963) observed a deterioration of choice discrimination (for colour and letters) at a COHb level of less than 5%, with parallel changes in cognitive ability (mental arithmetic, plural noun underlining and t-crossing). Horvath et al., (1971) saw a worsening of visual vigilance in nonsmokers at an average COHb level of 6.6%, and Ramsey (1972) described a small deterioration in reaction times at a COHb level of 5%.

Many authors seem prepared to accept the evidence of some deterioration of psychomotor function at a COHb level in blood of 3 to 4%, but the loss of auditory duration discrimination reported by Beard and Wertheim (1967) is more controversial. COHb was not determined in their original experiments, but from CO pressure (5 Pa) and exposure time (total 2 1/2 hr. a figure of 2 to 3% COHb was estimated. Attempts to replicate these experiments have generally been unsatisfactory (O'Donnell et al., 1970; Stewart et al., 1970; Weir et al., 1973; Otto et al., 1978; Wright and Shephard, 1978), although Beard and Grandstaff (1975) have presented further evidence of impaired time estimation at a COHb level of 2 to 3%.

Disagreement concerning the existence and level of a "threshold" is perhaps not surprising. In any psychomotor experiment, much depends upon "incidental" details of the working environment, the characteristics of subjects and the complexity of the test that is being performed. When testing mental function, it is important to utilize "spare" mental capacity. Firemen (Schulte, 1963) are perhaps more likely to show inaccuracies in simple mental arithmetic than are U.S. Air Force personnel (O'Donnell et al., 1971), and it seems significant that positive findings have usually involved the general population, while negative findings have been based on university students or military personnel where interest and peer pressure may be greater (Beard and Grandstaff, 1972). If aging and oxygen want are related (McFarland, 1963), performance changes caused by a CO induced "hypoxia" may be more readily apparent in those who are older. Changes in sensory performance (such as thresholds and duration discrimination) have also been detected more easily than changes in complex cerebral function or response. Changes in these latter two categories of performance influence the execution of a well-learnt task (McFarland, 1973). McFarland (1932; 1937a,b) further reported differences between "sudden" exposure (in the order of minutes) to hypoxic hypoxia and prolonged exposure (with opportunity for adjustment of the cerebral circulation and other variables to the CO poisoning). Finally, both Fodor and Winneke (1972) and Weir et al., (1973) suggested that the decrement in psychomotor performance was not linearly related to COHb levels. The results of Beard and Wertheim (1967) and Fodor and Winneke (1972) suggest that effects are greatest around 90 minutes after CO exposure.

9.2 Animal Experiments

It is always difficult to extrapolate toxicological data from animals to man. Patterns of uptake, distribution and elimination of pollutants show substantial interspecies differences, and it is uncertain whether target organs differ qualitatively or quantitatively in their sensitivity to the substance under investigation. The use of "nonverbal" animals

to test behavioural changes during CO exposure is particularly questionable. For example, does a reduction in the number of bar presses made by white Lewis strain rats exposed to 20 Pa CO for 2 hours (Goldberg and Chappell, 1967) indicate a change in biological function, a modification of a learned response, a reversal of a previously learned discrimination, or a decrease in feeding activity? Despite such uncertainties, studies on animals do suggest certain gross effects of CO, indicating changes which may merit further investigation in humans. For example, Beard and Wertheim (1967) observed that early in the course of CO exposure, rats exhibited what seemed to be a derangement of time sense. Therefore, a test of auditory duration discrimination was developed for human use. Again, studies with adult Macaca mulatta monkeys permitted Back and Dominiquez (1968) and Back (1969) to investigate whether long-term exposure to CO influenced CNS responses, an experiment for which there are few "volunteers". The task required of the animals (response to visual and auditory stimuli) was not very complicated; indeed, it became almost automatic with practice, and may thus have lacked sensitivity to any behavioural changes induced by the CO exposure. However, the results indicated that animals continued to perform single learnt tasks at COHb levels as high as 30% saturation (Theodore et al., 1971). Finally, animal studies allow direct measurement of cerebral blood flow (affected more by high COHb levels than by equivalent oxygen lack (Traystman and Fitzgerald, 1977), and brain-stimulation reinforced responses (affected equally by high CO pressures and oxygen lack, Annan, 1974).

9.3 Visual System

Discrimination and adaptation are basic properties of receptor systems. For the visual system, these properties comprise the following functions: (1) discrimination of spatial extent (visual acuity); (2) discrimination of intensity (differential brightness sensitivity); (3) temporal discrimination (critical flicker fusion); and (4) adaptation to low intensities of illumination. A number of authors have reported visual impairment at quite low COHb readings, although our Toronto laboratory observed no change of night vision, glare vision, glare recovery or depth perception with a 3.4% increase of COHb (Wright et al., 1973).

9.3.1 Visual Acuity

Stewart et al., (1970) found that eight hours exposure to 10 Pa CO (11% to 13% COHb) did not impair the visual acuity of 18 healthy men. Beard and Grandstaff (1970a) found a 5% reduction of visual acuity after 27 minutes of exposure to 5 Pa CO (a COHb level of 3% saturation estimated from alveolar gas); he used the more precise psychophysical testing technique of limits (Corso, 1967). Greater decrements of acuity (16% and 32%) were found at estimated COHb levels of 6% and 10% saturation. During exposure to

hypoxia, McFarland and Halperin (1940) found a significant rightward displacement of the visual acuity curve along the illumination (log photon) axis at a simulated altitude of 3050 m (~ 14.1 kPa O_2). Likewise, decrements of visual sensitivity were seen at COHb levels as low as 4.5% (McFarland et al., 1944), recovery lagging behind CO elimination. McFarland and his colleagues noted a progressively smaller decrease of log visual acuity as long intensity increased. It is thus possible that some of the discrepancies between CO studies can be explained by differences in the intensity of illumination. McFarland et al., (1944) also used a small sample of well-trained subjects, which reduced the risk of a "Type II" error arising from inter-subject variability of response.

9.3.2 Intensity Discrimination

McFarland et al., (1944) and Halperin et al., (1959) used the visual discriminometer developed by Crozier and Holway (1939) to test differential light sensitivity in a dim and uniformly illuminated field. Ten measurements were made of the least intensity which could be distinguished. Generally, response to a given increment of COHb was about the same as that seen with an equivalent reduction of arterial oxygen saturation produced by breathing low percentages of oxygen. The apparatus was sensitive enough to demonstrate an effect from one cigarette (a 2% COHb level). More recently, Beard and Grandstaff (1970a) reported a statistically significant increase in the threshold for visual intensity discrimination within 49 minutes of exposure to 5 Pa CO (COHb of 3% estimated from alveolar samples). The increased threshold was also observed 17 minutes after exposure to either 15 or 25 Pa CO. Weir et al., (1973) did not find any effect at 7% and 14% COHb; however, their visual test was brightness matching of three pairs of coloured lights. Likewise Ramsey (1972, 1973) found no effect of quite high levels of COHb (9-16%) upon brightness discrimination and depth perception.

9.3.3. Temporal Discrimination

Temporal discrimination, or alternatively the illusion of steady light, is commonly measured by the critical flicker fusion test (C.F.F.). The results depend on such physical relationships as: the intensity of the source relative to surrounding illumination, and the area, shape and location of the test patch. Anatomical and physiological determinants include: physique, size of pupillary opening, chronological age, body temperature and fatigue. Psychological variables include practice, learning and motivation (Landis, 1954). In view of the number of factors involved, it is not surprising that there is some disagreement concerning the effects of CO on CFF. Lilienthal and Fugitt (1946) found that combined exposure to a simulated altitude of 1524 to 1829 m and an increase in COHb of 5% to 9% saturation produced an impairment of CFF; however, COHb levels of

13.8% to 17.4% at sea level did not change the CFF over a 20-minute test period. Vollmer et al., (1946) found an insignificantly greater effect with 12% COHb and altitude (4724 m) than with altitude alone. Given the persistence of CO in comparison to hypoxia (Halperin et al., 1959), their technique of baseline determination (average of initial and final performance) could have obscured a CO response. However, more recent reports including Guest, Duncan and Lawther (1970); O'Donnell et al., (1971a); Ramsey (1972); Winneke (1974) and Weber et al., (1975) have found no changes in CFF at COHb levels of 9 to 16% saturation.

Nicotine and CO have opposite effects on CFF. Most studies of smoking (Barlow and Baer, 1967; Fabricant and Rose, 1951; Garner, Carl, and Grossman, 1954; Larson, Finnegan and Haag, 1950; Warwick and Eysenck, 1963) examined the effect of nicotine on CFF and did not measure blood COHb levels. Likewise, smoking was not specifically controlled prior to testing in some of the reviewed studies.

The auditory duration discrimination test (below) is a special case of temporal discrimination.

9.3.4 Dark Adaptation

Abramson and Heyman (1944) measured visual sensitivity before and after 20 minutes of CO exposure. Threshold values increased in 7 of 9 subjects at 10% COHb, but individual variability was such that no relationship between the CO content of the blood and diminution of dark adaptation could be described. Inter-subject and intra-subject variability also contributed to the negative findings of Weir et al., (1973) at 7% and 14% COHb and McFarland (1973) at 11% and 17% COHb.

9.3.5 Visual Evoked Response

Xintaras et al., (1966) reported alterations in the visual evoked response of rats with CO exposure. In man, no changes of the visual evoked response have been observed until COHb levels were greater than 20% (Hosko, 1970; Sprout, Neeld and Woessner, 1975); indeed, Dinman (1969) found no change of latency or voltage with a COHb level of 37%. Furthermore, COHb levels of 33% did not alter spontaneous EEG (electroencephalogram) activity (Hosko, 1970).

9.4 Auditory System

Frequency and intensity are the physical attributes which together or separately arouse the sensations associated with sound (Wyburn, Pickford and Hirst, 1964). Changes in the intensity threshold, intensity discrimination, frequency discrimination or sound localization with CO exposure have not been investigated. However, studies have been

conducted on auditory duration discrimination and auditory flutter fusion (AFF), some of which have reputedly demonstrated a deterioration of function at 2 to 3% COHb.

9.4.1 Auditory Duration Discrimination

The auditory duration discrimination task designed by Beard and Wertheim (1967) required the comparison of paired presentations of pure 1000 Hz tones. The mean percent correct responses decreased from 78% to 68% after 90 minutes exposure to 5 Pa CO (Coburn, 1979, has predicted from this exposure a COHb level of 2.5 to 4%). Beard, working with Grandstaff (1970b), was himself unable to replicate this result using paired visual signals, despite exposure to 25 Pa CO. In the second experiment, Beard and Grandstaff (1970b) avoided the range ± 125 milliseconds where discrimination would be difficult, if not impossible (Wright and Shephard, 1978c).

Both O'Donnell et al., (1971) and Theodore et al., (1971) suggested that the effect reported by Beard and Wertheim (1967) was due to sensory isolation. Their subjects were exposed to 7.5 or 15.0 Pa CO for 7.5 hours, with final COHb readings of 5.9 and 12.7% respectively. Unfortunately, the design of the experiment (an incomplete Latin square) did not allow comparison of CO exposure with air breathing. Further, details of the rate of signal presentation were not given. However, scores for signal detection did not differ at 5.9 and 12.7% COHb. Stewart et al., (1973) exposed subjects five at a time, allowing interaction between them for part of every hour. Using a double-blind protocol, they found no change of performance following exposures to 5, 10, 20 or 50 Pa CO for 2.5 or 5.0 hours. The task that they used was not an exact replicate of Beard and Wertheim's, since the second tone followed the first by 1.5 seconds rather than 0.5 seconds. In addition,the test was performed only once per hour (rather than every 20 minutes), with other tasks being performed in the intervening period. The former point is important, since systematic fading of an auditory image occurs over time (Corso, 1967; Massaro and Kahn, 1973; Plomp, 1964), while increased sensory stimulation sustains arousal (Beard and Grandstaff, 1972; Fodor and Winneke, 1972) with beneficial effects on vigilance (Wright, 1971). In support of this view, Stewart et al., (1973) noted that 9 subjects confined to an audiometric booth showed a significant (2.9%) decrement of signal detection at 9.7% COHb. Wright and Shephard (1978c) repeated Beard and Wertheim's 1967 experiment, using a "bolus" CO exposure, and they found that the most significant variable was time on the task. The simplest analysis of their data indicated a significant increase of mean errors at blood COHb levels as low as 3.2%, the dose/response line running in between the lines of Beard and Wertheim (1967) and Stewart et al., (1973).

Beard and Wertheim's 1967 test protocol presented the stimuli to the subjects using the psychophysical method of constant stimulus differences. This method is a more appropriate measure of auditory duration discrimination than an analysis based on the percent correct responses. When Wright and Shephard (1978c) applied this psychophysical method of analysis to their data, the previously observed CO related changes in performance were no longer evident. Thus, the generality of Beard and Wertheim's 1967 results cannot be supported. Indeed, if this is accepted as the optimal method of analysis, the results of our laboratory would confirm the claim that auditory duration discrimination is not impaired at COHb levels below 8% saturation. Otto et al., (1979) likewise observed no response to COHb levels of 7.8%.

9.4.2 Auditory Flutter Fusion

Variables affecting detection of auditory flutter fusion (AFF) are similar to those for the detection of visual flicker, namely intensity rate and sound-time fraction (Millar and Gregory, 1972). No reduction of AFF threshold has been observed at COHb levels up to 10% (Guest et al., 1970).

9.5 Cerebral Efficiency

Cerebral efficiency denotes the ease with which sensory information is processed; that is, the responsiveness of the central nervous system to sensory information, the processing of this information and a decision about the direction in which a response should occur. This rubric therefore encompasses vigilance, time estimation, learning and memory, mental and cognitive performance and choice reaction time.

9.5.1. Vigilance

Several authors have reported a deterioration of auditory or visual vigilance at quite modest COHb levels. Lewis et al., (1970) made no attempt to define the factors responsible for a decline of auditory vigilance observed when subjects breathed air pumped from the side of a moderately busy arterial road; CO pressures were apparently above 1 Pa 40% of the time, and over 3 Pa 4% of the time. Groll-Knapp et al., (1972) used an auditory vigilance test (detection of "slightly weaker tones") over 90 minutes exposure to 5, 10 or 15 Pa CO. They observed a progressive deterioration of performance, with changes in associated brain wave potentials. COHb was unfortunately not measured, but probably reached about 3.0, 5.4 and 7.6%. Haider et al., (1975), working in the same laboratory, were unable to replicate these observations. Fodor and Winneke (1972) used a similar type of test and found a substantial deterioration in signals detected after

80 to 110 min of exposure to CO (5 Pa, equivalent to a blood COHb content of about 2.3-3.1%). However, the effect disappeared as the exposure continued. Winneke (1974) carried out further observations at CO pressures of 5 and 10 Pa; although the COHb levels probably reached 9%, there was a small (insignificant) improvement of signal detection, in contrast to the errors observed during methylene chloride exposure.

Horvath et al., (1971) used an analogous visual vigilance test (detection of a slightly brighter light pulse). Subjects breathed air containing CO pressures of 2.6 Pa, and 11.1 Pa for 60 min. A significantly smaller number of signals were detected at 11.1 Pa (average COHb level for 10 nonsmoking subjects about 5%); however, the effect was not observed when the signal rate was increased from 2 to 10 per 3-minute interval. Beard and Grandstaff (1972) required their subjects to report shorter light pulses. They worked in an audiometric booth, with exposure to 5, 17.5 or 25 Pa CO; COHb levels rose from less than 1% to 1.8, 5.2 and 7.5% respectively over a 50-min exposure period. Signal detection deteriorated significantly at the two lower doses of CO, but returned almost to normal at 7.5% saturation (a finding reminiscent of Fodor and Winneke, 1972). The signal detection parameter d' (discriminability) decreased at the two lower doses, while β (subject's criterion, a measure of caution) increased. Arousal level is critical in vigilance studies. Winneke et al., (1976) were unable to replicate the findings of Horvath et al., (1971) with conditions that avoided sensory deprivation. Others in the Horvath laboratory (Christensen et al., 1977) also failed to show a deterioration of visual vigilance at 6% COHb when exposures were conducted in a clear plastic chamber, while Benignus and Otto (1977) found no deterioration in performance of a visual numeric monitoring task for COHb increases of up to 12.6%.

9.5.2 Time Estimation

Time estimation tasks have some affinity with the auditory duration discrimination tests already discussed, but rely on internal time cues. Sollberger (1967) has distinguished between a time duration sense (which would need only interval timers) and a time or orientation sense (which would use true chronometers). On this basis, time estimation could be regarded as distinct from auditory duration discrimination.

Beard (1969) had 7 subjects: (a) hold down a button for an estimated 30 seconds and (b) touch the same button at 10 second intervals. Estimation of the 30 second period was significantly impaired after 75 minutes of exposure to 5 Pa CO (a predicted COHb of less than 3% saturation) but deterioration in estimation of 10-second intervals was insignificant. Beard and Grandstaff (1972) confirmed the increase in 30-second time estimation with a 5 Pa CO exposure, but also found a significant increase in 10-second estimation.

Stewart et al., (1970), O'Donnell et al., (1970); Mikulka et al., (1970), and Weir et al., (1973) all included short (i.e., 10 seconds or less) time estimation tasks in their experimental protocols. No "feedback" of accuracy was given to the subjects. Further, they were allowed to walk around and stretch between tests to minimize fatigue and boredom. Weir et al., (1973) were the only group who found a significant change (a reduction rather than an increase, and then only at a COHb level of 20% saturation). Both O'Donnell et al., (1971) and Stewart et al., (1973) observed a significant increase in the 30-second estimation at 9.4% COHb, but only during sensory isolation. Thus it is likely that Beard's 1969 and Beard and Grandstaff's 1972 results are attributable to boredom and sensory deprivation, a consequence of the fact that they had their subjects perform only one repetitive task throughout their experiment.

9.5.3 Learning and Memory

Both Beard and Grandstaff (1972) and Wright (1976) have found that 7.5% COHb does not change the short-term retention of digits. In contrast, Bender et al., (1971) found a significant decrease in backwards (but not forwards) retention of digits, as well as a significant increase in the time to memorize meaningless syllables at a COHb level of 7.2%. The meaningless syllable task involves long-term memory stores, as does digit reversal (Fitts and Posner, 1967). Apparently short-term memory is not impaired by CO, but long-term memory is affected.

9.5.4 Mental and Cognitive Performance

There is still much to be resolved concerning the effects of CO on mental and cognitive performance. Schulte (1963) found a significant correlation between mental performance and exposure to CO, with marked loss of speed on such tests as responding to letters and colours, underlining plural nouns, crossing t's and arithmetic ability at a COHb of about 8%; however, the accuracy of the measured blood COHb levels has been questioned, since initial COHb readings were close to 0% even in smokers (Beard, 1969; O'Donnell et al., 1970). Similarly, interpretation of the study of Lewis et al., (1970) is uncertain, for although they found significant increases in the time required to perform both arithmetic and comprehension, they did not measure the CO content of the roadside air. O'Donnell et al., (1971a) did not find a significant deterioration of mental arithmetic at COHb levels as high as 12.7%, although times were 10% slower at 15 Pa than at 7.5 Pa CO. Nevertheless, their subjects were few (n of only 4) and specialized (altitude trained) relative to the firemen tested by Schulte (1963). Small and unreliable changes of sleep were considered as possible evidence of reduced central nervous

activation (O'Donnell, 1971a). Bender et al., (1971) found a significant deterioration in letter identification, memorization of meaningless syllables and digital reversal at 7.2% COHb (10 Pa CO). However, no differences were observed in other tests such as problem calculations, analogies and shape selection, and all changes were insignificant at a lower COHb level (4.9% saturation, Fodor and Winneke, 1972). Finally Beard and Grandstaff (1972) did not observe any change in performance of a visual search and selection task at COHb levels of 7% and 8%.

9.5.5. Choice Reaction Time

Choice reaction time, unlike simple reaction time, requires a decision before a response can be initiated. Ramsey (1970, 1972, 1973) used this task as a measure of changes in CNS function in both healthy adults and in those with a health handicap. Reaction times were significantly slower (Ramsey, 1970) after 90 minutes exposure to congested traffic (3.8 Pa CO, estimated COHb levels of 3.5% to 4.0%). In a subsequent study (Ramsey, 1972), the increase in reaction time at 5% COHb was significant only when data from normal, emphysematous and anaemic subjects were grouped together. In healthy individuals (university students), Ramsey (1973) found a decrement in choice reaction time with 45-min exposures to 65 or 95 Pa CO (blood COHb levels of 7.6 and 11.2%). Fodor and Winneke (1972) found no change at a COHb level of 5.3%.

9.6 Psychomotor Performance

A factorial breakdown of psychomotor performance has been described by Fleishman (1954). The present review in general follows his plan, but the order has been changed to accommodate the two main groupings of speed and precision, as suggested by Fodor and Winneke (1972). Because of the multi-factorial nature of skilled performance, many authors have used extensive test batteries, allowing multiple comparisons between CO and air. Unfortunately, statistical analysis has not always made appropriate allowance for such comparisons by use of multivariate techniques or insistence upon conservative probability thresholds.

9.6.1 Speed of Movement

No CO-related performance deterioration in wrist or finger movement was observed at COHb levels of up to 20% (Fodor and Winneke, 1972; Sayers et al., 1929; Weir et al., 1973). Fodor and Winneke (1972) also found no CO related effect on the rate of arm movement at COHb levels up to 5.3%. Several authors have observed no significant effect of CO on simple reaction time with a COHb increase of 3.4% (Wright et al., 1973), an increase of 6 to 8% (Rummo and Salarnis, 1974), levels up to 16% (Stewart et al.,

1970) and levels up to 20 to 30% (Sayers et al., 1929). One discordant report by Ramsey (1972) has appeared. His subjects included 20 normal subjects, but also 20 patients with "mild anaemia" and 20 patients with emphysema. After a 45-min exposure to 30 Pa CO (COHb about 4.5%) there was a small but statistically significant increase in "reaction time to a visual stimulus"; it is probable that this task involved an element of choice i.e. it was a complex reaction time).

9.6.2. Precision of Movement

Most experiments involving coordination, tracking, steadiness and dexterity tests have proved negative. The tests for Singer dexterity involved grasping, release, manipulation and assembly of small objects, as in the Crawford collar and pin test (Stewart et al., 1970) or the Purdue Pegboard test (Bender et al., 1971; Fodor and Winneke, 1972); the skills required are finger dexterity and hand-eye coordination. Fodor and Winneke (1972) did not find a significant impairment at COHb levels of up to 5.3%, but Bender et al., (1971) noted a significant deterioration after 3 1/2 hours exposure to 10 Pa CO (an average COHb of 7.2% saturation). Stewart et al., (1970) reported a significant correlation between the decrease in performance and CO exposure (2.5, 5.0 and 10 Pa CO for eight hours), but considered this relationship spurious.

No CO related effect on controlled manual dexterity was observed at COHb levels of up to 20% saturation (Fodor and Winneke, 1972; Weir et al., 1973), and no effect on manual dexterity was found at levels of up to 13% saturation (Stewart et al., 1970).

Dorcus and Weigand (1929) found some impairment of arm-hand steadiness with 5 hours of exposure to 40 Pa CO. However, no significant effect was demonstrated at COHb levels of up to 13% (Stewart et al., 1970), or 20 to 30% (Sayers et al., 1929). Replication of the experiments at lower CO pressures may be desirable, since Fodor and Winneke (1972) found a marginal effect ($P < 0.10$) at a COHb level of 5.3%, while Johnson et al., (1974) observed a deterioration of hand-eye coordination in toll-booth operators exposed to CO.

Fodor and Winneke (1972) found no effect on psychomotor coordination at a COHb level of 5.3%. O'Donnell et al., (1971) used a tracking task where a needle had to be kept within prescribed limits on a dial for 1-minute while monitoring three other dials. No effects were observed at COHb levels up to 12.7%. In a second version of the test, the corrective movements became more difficult with time, and note was taken of the period for which subjects could cope with the task (Mikulka et al., 1970). A transient deterioration of performance was observed after two hours of exposure to 5.0 or

12.5 Pa CO (final COHb 3 or 6.6%). However, the authors concluded that the effect was not statistically significant, and Hanks (1970) found no deterioration in performance of the same task with 4 1/2 hours of exposure to 10 Pa CO.

No ataxia or deterioration of postural control was observed at COHb levels of up to 20% (O'Donnell et al., 1971; Weir et al., 1973).

9.7 Driving of Vehicles

Considering that the automobile is the prime source of ambient carbon monoxide, it is not surprising that performance assessments have been gradually extended to include driving simulators and "on-the-road" tests. A deterioration of driving skills could have important consequences, both in its own right and as a cause of vehicular accidents. Unfortunately, the results obtained have come under serious criticism, due to incomplete publication, weaknesses of experimental and statistical methodology, and limited relevance of the usual simulators to the normal driving situation. Nevertheless, one merit of certain test devices is a need for continuous attention. This places a high level of demand upon the central nervous system, using up "spare" mental capacity (Ashton et al., 1972a, b). The importance of spare capacity should not be underestimated.

Forbes et al., (1937) increased COHb levels by as much as 30%, and then examined reaction times, coordination and perception in the context of driving. The authors commented that although their subjects could concentrate long enough to perform a psychomotor task reasonably well, they were subjectively aware that their driving ability was impaired. The data of Rockwell and his associates (Ray and Rockwell, 1970; Rockwell and Ray, 1967; Rockwell and Weir, 1975) suggest that driving ability may be impaired, but high COHb levels were reached (10-20%) and the results remain largely in a preliminary format. Wright et al., (1973) examined a mixture of smokers and nonsmokers, adopting a single-blind "bolus" exposure sufficient to increase blood COHb levels by an average of 3.4%. Scores for a number of measures of careful driving habits showed small deteriorations of function following CO inhalation. However, changes were not significant, based on a conservative statistical analysis. Rummo and Sarlanis (1974) used a simulator that tested responses to slowing of the lead car. Subjects described the procedure as "realistic but boring". There was a deterioration of several performance measures with a 6 to 8% increase of COHb (exposure to 80 Pa CO for 20-min.); response times were slowed and steering reversals decreased, but changes were only significant if data for one smoker were excluded.

The "on-the-road" studies of Weir et al., (1973), McFarland (1973), Ray and Rockwell (1970), Rockwell and Ray (1967) and Rockwell and Weir (1975) support the view that CO exposure can affect road safety. Spare mental capacity was reduced through visual occlusions and steering wheel reversals provided an objective measure of driving control. Weir et al.,'s data revealed perceptual narrowing with increased COHb levels (7% and 12% saturation); there was also a reduction in the number of glances into mirrors prior to leap-frog passing, increased variations in vehicle speed, decreased ability to control following distance and decreased steering motions at COHb levels of 12%. McFarland (1973) found that subjects required significantly more roadway viewing at 80 km/h with a COHb level of 17% saturation than they did with a nominal COHb level; however, in their experiments there was no change in the number of steering wheel reversals.

10. ADAPTATION TO CARBON MONOXIDE EXPOSURE

10.1 Short-term

Possible short-term adaptations lessening the toxicity of a given CO exposure include increases of coronary and cerebral blood flow. We have already noted some experiments where an effect of CO was observed at low levels of COHb, early in exposure, but this response disappeared as the experiment continued.

Animal experiments give clear evidence for the increase of coronary blood flow (Ayres et al., 1970; Young and Stone, 1976), thus raising the possibility that there is one segment of the population (those with coronary atherosclerosis) who are less able to make short-term adaptations to high CO concentrations.

10.2 Long-term Acclimatization

Haldane and Priestley (1935) and Killick (1936) reported a considerable degree of acclimatization to CO in humans, with a lessening of symptoms, a slower heart rate and a 30 to 50% reduction in equilibrium COHb% during successive exposures to the same concentration of CO. At the time of these investigations, an active transport of CO and/or oxygen was postulated to occur at the alveolar membrane. However, methods of measuring COHb were crude, and technical problems may have led to these findings. Animal experiments (Clark and Otis, 1952; Gorbatow and Noro, 1948; Killick, 1937; Zebro et al., 1976) also show evidence of considerable long-term adjustments to CO. Surprisingly, Killick (1936) observed no increase of red cell count or haemoglobin concentration. However, polycythaemia has commonly been observed (see for example Brieger, 1944; Hahn-Pedersen, 1962; Syvertsen and Harris, 1973; Theodore et al., 1971). Vernot et al., (1970) exposed Rhesus monkeys and Beagle dogs to 5 to 50 Pa CO for 11 to 26 weeks; the red cell counts, haemoglobin concentrations and haematocrits started to increase during the first week of exposure, and stablized at an elevated level after one month of exposure. The polycythaemia was normocytic, normochromic, and a linear function of the CO concentration used. Jones et al., (1971) observed an increase in haemoglobin content and haemoglobin in rats, guinea pigs, monkeys and dogs exposed to 9.6 and 20 Pa CO 8 hours per weekday for a total of 90 days. However, changes did not occur at 5.1 Pa CO. The concept of a dose-response threshold is supported by negative findings in monkeys with COHb levels of 8% (Eckardt et al., 1972), but positive findings after 3 weeks at 10 to 15% COHb (De Bias et al., 1973). In humans, data from smoking withdrawal clinics (Rode, 1970) suggest a development of polycythaemia in response to a habitual 7% COHb saturation, while reports from Mexico City indicate that a 7 to 8% drop in arterial oxygen

saturation induces polycythaemia over a period of at least two to three weeks (Shephard, 1970). The process seems relatively slow, in that Kjeldsen and Damgaard (1968) found no increase with 8 days of intermittent exposure to 500 Pa CO (mean COHb level, 13%).

It has been reported that the red blood cell concentration of 2, 3-diphosphoglycerate (DPG) decreases with quite brief (24-hr) exposure to high pressures of CO (COHb > 20%) (Åstrup, Kjeldsen and Wanstrup, 1970). This effect is associated with an increased affinity of haemoglobin for oxygen and a displacement of the O_2Hb dissociation curve to the left (the Haldane effect). Others find no change (Mulhausen et al., 1968; Radford and Kresin, 1973) or an increase (Dinman et al., 1970). With hypoxic hypoxia, the O_2Hb dissociation curve shifts to the right; this change is associated with elevations of red cell 2, 3-DPG concentrations (Benesch and Benesch, 1967). The exact mechanism must yet be clarified; it is possible that high COHb levels (20% and greater) produce a decrease in 2, 3-DPG, while lower COHb levels (16% to 20%) increase 2, 3-DPG concentrations (Dinman, Eaton and Brewer, 1970).

11. INTERACTIONS

11.1 High Altitude

A substantial fraction of the world population lives at high altitude. There has been little study of CO toxicity in high altitude natives, where risks may be ameliorated by acclimatization to hypoxia (Master, 1976; Weiser et al., 1979). However, there are now many middle-aged vacationers who visit high regions of the world. In such locations, cold and reduced compression of car engines plus narrow mountain valleys may encourage the accumulation of high CO concentrations. Hyperventilation favours both absorption (Forbes et al., 1945) and subsequent elimination of CO, but retention is favoured by the lower partial pressure of oxygen. The resultant elimination rate is thus relatively independent of altitude, at least to 3000 metres (Gorodinsky et al., 1970).

Both Forbes et al., (1945) and Lilienthal et al., (1946) considered COHb equivalents resulting from a combined exposure to altitude and CO. McFarland et al., (1944) developed "physiological altitudes" dependent on actual altitude and % COHb. Both authors considered fairly high altitudes (1500 - 5000 metres). The reduction in visual intensity discrimination produced by a given increment of % COHb was equal to that elicited by the same decrement in % O_2Hb. Pitts and Pace (1947) based their comparisons on heart rate at altitudes of 2000 to 3000 metres. They estimated that a 1% increase of COHb was associated with a 108-metre increase of altitude. The implication might seem to be that an increase in altitude of 1000 metres produces a baseline 9% increase of COHb. However, more recent studies suggest that the hypoxic effect of altitude is nonlinear, with little physiological reaction below 2500 m (Buskirk et al., 1967). The reason for this threshold is the sigmoid shape of the oxygen dissociation curve of haemoglobin (Ernsting and Shephard, 1951), and it is not clear how far the altitude threshold might be modified by CO-induced changes in the shape of the oxygen dissociation curve.

11.2 Other Air Pollutants

Carbon monoxide may react with and alter the concentration of other pollutants in the atmosphere. However, evidence of biological interaction with other pollutants is less convincing. Animal experiments have suggested the possibility that 5 Pa of CO exerted additive effects with NO_2 (Bussey, 1972; Nakajima et al., 1972) and ozone (Murphy, 1964). In man, there was no interaction between CO (3-5 Pa) and peroxyacetylnitrate (Drinkwater et al., 1974), SO_2 or ozone (Hackney et al., 1975), although there has been one report of enhanced toxicity in the presence of CO (1 mg/m^3), phenol and dust (Elfinova et al., 1972). The main theoretical basis for interaction would seem to be an increase

of mortality when CO poisoning was superimposed upon exposure to an agent that caused pulmonary oedema; in this situation, a further impairment of oxygen transport could be lethal. Road and rail traffic accidents arising during periods of dense particulate accumulation (a "London fog") might also be increased if the vigilance of vehicle operators was impaired by CO exposure. Although there are no good figures for such risks, they are unlikely to be the limiting factor in air quality decisions.

11.3 Drugs

In animal experiments, there has been some evidence that CO attenuates the effect of stimulant drugs (McMillan, 1974) and enhances the action of depressants (Montgomery and Rubin, 1971) including alcohol (Pankow et al., 1974). In man, alcohol apparently does not interact with CO, at least until COHb blood levels reach 12% (Rockwell and Weir, 1975; Stewart et al., 1974).

A reduced tolerance to CO poisoning might be anticipated in the 40% of the adult population who smoke, since cigarette smokers have COHb levels in blood of 5 to 10% saturation. However, many years of smoking have induced adaptive reactions such as an increase of haemoglobin level, and the only practical effect of atmospheric exposure is to slow the elimination of self-imposed pollution.

12. HIGH-RISK GROUPS

An important point of philosophy in air-quality decisions is that the permitted exposure be tolerated not only by the healthy young adult who is the normal experimental subject, but by high-risk segments of the population - the very young, the elderly, and the diseased.

12.1 Foetus, Newborn and Pregnant Women

Many authors have discussed the harmful effects of CO exposure upon foetal development (Åstrup et al., 1972; MacMahon et al., 1965) and perinatal mortality (Longo, 1977). Ethical considerations preclude deliberate administration of CO to pregnant women. Evidence is thus limited to animal experiments, occasional accidents, and women who smoke. In the last case, part of the apparent toxicity may relate to other constituents of the cigarette smoke, plus socioeconomic and genetic correlates of the cigarette habit.

In accidents and suicides, the pregnant woman herself has an increased susceptibility to severe CO poisoning (Smith et al., 1935), due to an increase of resting ventilation and anaemic tendencies (Hellman and Pritchard, 1971). Absorbed CO penetrates to the foetus unless the exposure is so severe that the mother is killed very quickly. Both the uptake and the elimination of CO proceed 2 to 3 times more slowly in the foetus than in the mother (Hill et al., 1977). Thus a transient CO exposure may yield lower peak COHb levels in the foetus than in the mother; on the other hand, the foetus may sustain higher 24 h average COHb readings. The harmful effects of a given COHb reading are greater in the foetus because (i) the arterial oxygen pressure is low, and (ii) there is little scope for compensatory adjustments in the foetal circulation. One study of sheep found that 57% of foetuses died when a foetal COHb level of greater than 15% was sustained for 30 minutes or longer (Longo, 1976). This is approximately equivalent to a 50% reduction of foetal blood flow (Hill et al., 1977). Engel et al., (1969) found somewhat less CO binding in foetal than in maternal haemoglobin, but Longo (1977) observed a 25% higher equilibrium COHb saturation in the foetus than in the mother (ratios ranging from 0.6 to 1.6). Harm may result not only from the impairment of oxygen transport, but also from impaired placental metabolism at a COHb level of 7%. The situation of the foetus is further compromised by a threefold increase of endogenous CO production in the pregnant woman.

There have been few studies on the newborn. When rabbits were exposed to fairly high CO levels (9 Pa) for 30 days (maternal COHb 9-10%), birth weights were decreased by an average of 11%, and the newborn mortality rate was more than doubled (Åstrup et al., 1972). When rats were exposed to high CO levels (15 Pa) throughout gestation, the birth

weight was somewhat reduced (3%), behavioural activity prior to weaning was lessened, brain protein levels were lowered, and neonatal weight gain was decreased (Fechter and Annau, 1976). High altitude impairs foetal development, with the possibility of additive effects from altitude and CO-induced hypoxia (New Mexico State Department of Health, 1975).

The possibility of more long-term effects of CO is raised by studies on the children of mothers who smoked 10 or more cigarettes per day during pregnancy. Reading attainment is impaired at the age of 7 (Davie et al., 1972; Goldstein, 1971), and at 11 years there is 3 months retardation of general ability, 4 months retardation of reading and 5 months retardation of mathematical ability (Butler and Goldstein, 1973). There has also been a report of minimal brain dysfunction (hyperkinesis) in the infants of mothers who smoke (Denson et al., 1975). If CO is indeed responsible for these effects, the critical COHb level remains uncertain; various studies have shown a maternal COHb averaging 4.1 to 6.7%, and a foetal level of 3.6 to 7.6% (Coburn, 1977).

Young children may be more vulnerable to CO than adults because of (i) a higher resting metabolism, and (ii) a greater level of habitual activity. However, the peripheral circulation is better in children than in adults. One study at a nursery in downtown Chicago noted an average COHb saturation value of 6.98% (Behrman et al., 1971).

12.2 Hypoxic Diseases

Individuals with impaired pulmonary oxygen uptake or reduced blood oxygen carrying capacity (anaemia, low cardiac output, decreased arterial pO_2) are at increased risk for a given CO exposure (Bartlett, 1968; Dinman, 1968; Permitt and Farhi, 1969). Problems are particularly likely if atherosclerotic disease prevents compensatory increases of circulation to skeletal and cardiac muscle. In the U.S., some reports suggest that atherosclerosis has a prevalence of about 12%, with a total of more than 20% of the population being affected by various cardiorespiratory disorders. Others set the prevalence of significant stable angina at no more than 2.1% (Moriyama et al., 1971). Several of the conditions mentioned give rise to hyperventilation, speeding CO uptake (Cropp, 1970). On the other hand, in chronic chest disease a reduced pulmonary diffusing capacity, increased erythropoiesis and a rightward shift of the oxygen dissociation curve may all give some protection against CO. One adverse factor in the chest patient is a greater than normal widening of alveolar-arterial oxygen difference. In a study of 10 patients with chronic obstructive lung disease, an increase of COHb from 1.5% to 4.1% saturation reduced the time to marked exercise-induced dyspnea by 33%; however, it was not established clearly whether the change of performance had a respiratory or a cardiac basis (Aronow et al., 1977).

In an anaemic individual, not only is there an initial impairment of oxygen transport, but a given CO pressure leads to a higher percentage COHb, with a correspondingly greater potential for extravascular escape of the carbon monoxide. Haemolytic disease of the newborn adds the further burden of increased endogenous CO production (Necheles et al., 1976; Oski and Altman, 1962).

12.3 Blood Transfusions

Blood donors who smoke may provide blood containing 10% COHb or more (Shields, 1971; Stewart et al., 1973a). This persists during storage (Millar and Gregory, 1972), and is a particular hazard for infants undergoing exchange transfusions (Kandall et al., 1973).

13. ACUTE AND CHRONIC TOXICITY

Severe exposures are of interest mainly as indicating potentially vulnerable systems, bringing to light changes that might pass unnoticed with lesser doses of CO.

13.1 Acute Toxicity

Early research (Dinman, 1974; Drinker, 1938; Grut, 1949; Haldane, 1895a; Haldane and Priestley, 1935; Killick, 1940; Silk, 1975) was concerned with the clinical effects of very severe carbon monoxide poisoning and suicide attempts. More recent reviewers have concentrated on specific hazards in fire fighting (Barnard, Gardner and Diaco, 1976; Burgess et al., 1977; Matromatteo, 1959a,b), aviation (Howlett and Shephard, 1973) and the home (Wright, Polk and Shephard, 1974).

Both Haldane (1895a) and Henderson et al., (1921) found that the symptoms associated with prolonged exposure to CO were related to the percentage saturation of haemoglobin with CO, i.e., problems were arising from oxygen want in the tissues. A brief exposure to a very high concentration of CO (35 kPa) produces a frontal headache and slight sagging of the ST segment of the ECG at a COHb% of approximately 10% (Stewart et al., 1973b). In the more usual forms of accidental poisoning, a blood COHb level of 20% is usually associated with headache, throbbing in the temples, some loss of manual dexterity, and dyspnea on exercise. At levels of 30 to 40% COHb, the headache becomes severe. Nausea, vomiting, dizziness and irritability are seen, vision may be disturbed, and the skin assumes a characteristic pinkish ("cherry red") hue, sometimes with areas of erythema. At levels of 40 to 50% COHb, dimness of vision, chest pain, an euphoric confusion, incoordination, and fainting on exertion are likely, while COHb concentrations greater than 50% are liable to cause unconsciousness, hyperpyrexia, convulsions, and even death. Some 8% of hospital admissions for CO poisoning have a fatal outcome (Davidson, 1970). At the highest concentrations (>50 kPa), death from cardiac arrhythmia may occur before there has been a substantial increase of the average COHb%, a "slug" of anoxic blood provoking ventricular fibrillation (DeBias et al., 1976). The organs most vulnerable to CO are the heart and the brain, the latter showing hyperemia, oedema, and petechial hemorrhages, with symmetrical softening of the lenticular nucleus (Longo, 1977). If the patient survives the acute episode, there may be after-effects. The electrocardiogram sometimes shows changes such as premature ventricular complexes, artrial fibrillation and ST abnormalities for several weeks, while an echocardiogram may reveal abnormal motion of the left ventricular wall (Corya, Black and McHenry, 1976); all of these changes suggest temporary or permanent myocardial injury. The brain, also, may suffer permanent damage (Shillito, Drinker and Shaugnessy, 1936; Smith

and Brandon, 1973), although the usual symptoms of such injury (personality change and memory disturbance) are hard to document in the absence of previous objective information regarding a patient; in one study, 39 of the 21 142 patients were subsequently confined to mental institutions (Hartmann, 1972).

13.2 Chronic Toxicity

The problems of assessing the chronic toxicity of CO are even greater than those associated with acute toxicity determinations; indeed, the very existence of a distinct syndrome of chronic carbon monoxide intoxication remains uncertain, at least for human subjects (Dinman, 1974).

Some animals such as rabbits are more vulnerable than others. In the rabbit, pathological changes have been reported with as little as 4 h exposure to 10 Pa. Findings have included hyaline degeneration of heart muscle with associated ECG abnormalities (Ehrch, Bellet and Lewey, 1944; Kjeldsen, Thomsen and Åstrup, 1974; Wanstrup, Kjeldsen and Åstrup, 1969), and degenerative changes in the cerebral cortex, limbic system and brain stem with related disturbances of posture, reflexes and gait (dogs exposed to 10 Pa CO for 11 weeks (Lewey and Drabkin, 1944)). Changes in the central nervous system could conceivably have been secondary to cardiac damage. In most animal experiments, impairment of cardiovascular and central nervous system function has been seen only with sustained COHb levels of 20 to 30%. However, Shul'ga (1961) reported an alteration of motor chronaxie and pathological changes in the central nervous system with the exposure of rats to a CO pressure of 2.5 Pa eight hours per day for 10 weeks. Neither the CNS damage nor associated changes in porphyrin levels were quantitatively documented. Preziosi et al., (1970) observed various brain lesions, an abnormal ECG and cardiac dilatation, with thinning, scarring and degeneration of the myocardium when dogs were exposed to CO pressures of 5 to 10 Pa for up to 6 weeks. Lindenberg et al., (1961) presented a report from the same laboratory, describing changes in right ventricular and arterial pressures of dogs with the same pattern of exposure. DeBias et al., (1976) observed an abnormal ECG and increased susceptibility to electrically induced fibrillation when Cynomolgus monkeys were exposed to a CO pressure of 10 Pa for 24 weeks. Increases of haemoglobin with chronic CO exposure have already been discussed. Penney et al., (1974) found cardiac hypertrophy in rats following 2 weeks of massive exposure (50 Pa CO).

Symptoms have been reported in man with a COHb% level of 5% (Grut, 1949). However, the complaints mentioned (headache, insomnia, fatigue, irritability, impairment of memory, confusion, dizziness, mood disturbances, cardiac symptoms, digestive disturbances, diarrhoea, hyperhidrosis, thirst and decrease of libido) are hard to evaluate, since the subjects, all drivers of producer-gas vehicles, knew they had been exposed to the gas. Lindgren (1961) compared exposed groups with controls taken from similar work; they also found more frequent headaches in exposed subjects, but the frequency of illness was comparable in exposed and control groups.

The most consistently noted physiological effect of long-term carbon monoxide exposure in man and in animals is a polycythaemia. Other reported long-term effects of CO include an increased reticulocyte count (Kjeldsen and Damgaard, 1968b) and serum cholesterol (Kjeldsen and Damgaard, 1968a), a leakage of albumin from the capillaries (Åstrup, 1972; Siggaard-Andersen et al., 1968), capillary patelet thrombosis (Niden and Schultz, 1965) and possible changes of electrolyte excretion (Paulie et al., 1968a,b) clotting time (Kalmaz et al., 1977; Sairo and El-Attar, 1968) and urine production (Kjeldsen and Damgaard, 1968b).

14. EVALUATION

Certain health aspects of acute and chronic poisoning have already been discussed. Sensitive groups comprise people with severe anemia, chronic pulmonary disease, atherosclerosis of the coronary and peripheral vessels, foetuses and newborn infants. Topics which will be considered in this section include interactions with ischemic heart disease, accidents and litigation. Anginal pain and cardiac deaths occur at particularly low CO pressures, and are probably the main factor forming the basis for air quality standards for CO.

14.1 Ischemic Heart Disease

14.1.1 Animal Experiments

Rabbits (Åstrup, 1969; Åstrup et al., 1967; Birstingl, Hawkins and McEwen, 1970; Kjeldsen, Wanstrup and Åstrup, 1968; Kjeldsen, Åstrup and Wanstrup, 1972; Thomsen and Kjeldsen, 1974; Wanstrup et al., 1969), squirrel monkeys (Webster, Clarkson and Lofland, 1968) and pigeons (Armitage, Davies and Turner, 1976) have all been reported to develop atherosclerosis in response to chronic carbon monoxide exposure. Nevertheless, the majority of papers are from one laboratory. Furthermore, in many, but not all of the experiments cited, it was necessary to feed a high cholesterol diet and to administer large doses of CO (20-30% COHb) in order to obtain positive findings. Cholesterol accumulated in the vessel walls, and there was an associated splitting of sub-intimal structures, with gaps between the cells, infiltration with lipid droplets and the development of oedema. Parallel changes can be induced by hypoxia (Boatman and Carter, 1973), and if 28% oxygen is administered in association with the carbon monoxide, lesions do not appear (Kjeldsen et al., 1968). The pathological significance of the findings is still debated. Possibly, CO increases the permeability of the vessel walls to lipid (Parving, 1972; Siggaard-Andersen et al., 1968), although lipase inhibition may also be involved (Kjeldsen and Damgaard, 1968a).

Other species (rhesus monkeys, baboons, beagle dogs, rats and mice) do not show atheromatous change after as much as 168 days exposure to 40 to 50 Pa (Theodore et al., 1971). Again, in Japan heavy smokers do not seem to have a high risk of either heart attacks or atherosclerosis (Kagan et al., 1974). The relevance of the positive findings on Scandinavian pigeons is thus doubtful for man, even if he is a heavy smoker with a high cholesterol diet. According to Tillmanns et al., (1975) CO exposure leads to a marked increase of cholesterol uptake in human coronary arteries perfused at postmortem, but changes seem most unlikely at usual urban CO pressures (0.1 - 1.0 Pa).

14.1.2 Epidemiological Studies

One group frequently exposed to high concentrations of CO are fire fighters. An early report (Dublin and Vane, 1947) suggested such men had the highest mortality index for cardiovascular and renal disease of any occupational group. A specific study of death certificates for 271 Canadian city firemen confirmed a highly significant excess of cardiovasular-renal mortality (Mastromatteo, 1959b), while stress testing disclosed a substantial proportion (10%) of ischemic exercise ECG's in Californian firemen (Barnard et al., 1976). However, in all of these studies it is difficult to assess the impact of other adverse aspects of fire fighting - a sedentary life, periodic stressful emergencies, and exposure to a wide variety of toxic agents.

In the Shinshu region of Japan, an open charcoal fire is commonly used to heat the rooms where tatami mats are manufactured. CO pressures average 7 Pa, with peaks of 30 Pa. The workers commonly have blood carboxyhaemoglobin saturation levels of 20-30%, and atherosclerotic heart disease is five times as common in this population as in residents of other parts of Japan (Komatsu, 1955).

Another potentially vulnerable occupational group are tunnel traffic police. Ayres et al., (1973) found an average COHb% of 2.9 ± 1.4% in nonsmoking tunnel workers (i.e. a figure 2-3 times the normal for a city dweller). Some 10% of the police showed an ischemic exercise ECG (more than expected), but the frequency of definite or possible heart attacks was no greater than would have been predicted from the age and constitutional makeup of the sample.

Gordon and Roger (1969) have commented on disturbances of cardiac rhythm in firemen following CO exposure, but details of the severity of exposure are lacking.

Californian investigators have sought to relate the normally modest urban CO exposures to cardiovascular deaths (Goldsmith and Landaw, 1968; Goldsmith and Aronow, 1975). One difficulty with this type of experiment is the uncertain lag period between exposure to pollutant, prodromal symptoms and the definitive heart attack. Choen, Deane and Goldsmith (1969) examined admissions to 35 Los Angeles hospitals. No association was found between atmospheric CO in the vicinity of a given hospital and the number of admissions for myocardial infarction. However, the case fatality rate was related to atmospheric CO on the day of admission in areas of high pollution (weekly average > 0.8 Pa CO). Unfortunately, the effect was due more to a reduction of deaths in the area of low pollution (case fatality 27 → 20%) than to an increase in the area of high pollution (case fatality 26 → 30%). Furthermore, any effect could have arisen from inter-hospital

differences in patients admitted or standards of medical care. Against this possibility, the effect was only seen in the winter months, when pollution was high. Spurious correlation could still be attributed to seasonal factors such as an influenza epidemic or even a variation in available hospital beds (since many heart attacks occur outside the hospital system). To counter this possible criticism, Hexter and Goldsmith (1971) related daily deaths to environmental pollution by a sophisticated multiple regression equation, using day numbers for trend and harmonic terms for cylic variations in such variables as season, temperature, and oxidant air pollution. The residual effect was relatively small, and could have arisen from some unmeasured air contaminant other than CO. However, Hexter and Goldsmith (1971) concluded that if the 24-hr average CO pressure increased from 0.73 Pa to the very high figure of 2.02 Pa, this would produce 11 excess daily deaths in the Los Angeles area; further, the effect would disappear if deaths from cardiovascular disease were excluded. Curphey et al., (1965) made postmortem tests on 2207 deaths in the Los Angeles area, but found no relationship between COHb levels and the cause of death. Kurt et al., (1978) found an increase of cardiorespiratory complaints in the emergency room of the Colorado General Hospital if the CO pressure exceeded 0.5 Pa (24-hour average) or 1.1 Pa (one-hour average). However, COHb levels were not measured, and CO pressures were recorded from only one monitoring station; furthermore, high altitude (about 1500 metres) may have increased the sensitivity of this population to CO. An investigation from the John Hopkins Hospital had the advantages of a clearly-defined population and well-established diagnoses, but unfortunately for the study, CO exposures were measured at only one sampling station and were relatively light (partial pressures in the range 0-0.4 Pa compared to > 0.9 Pa). With this level of pollution, there was no "clustering" of myocardial infarctions or heart attacks on days when CO readings were increased (Kuller et al., 1975). Postmortem COHb readings were higher in arteriosclerotic heart disease deaths than in controls, even when smokers were excluded. However, this finding seemed due to the inclusion of patients with smoking-induced disease or a continuing unreported cigarette habit, since the difference disappeared when ex-smokers were excluded from the analysis.

Wald et al., (1973) examined the prevalence of arteriosclerotic heart disease among smokers; a relationship to COHb levels was seen, even after the data had been adjusted for age, sex, duration of smoking, serum cholesterol and reported cigarette consumption. However, it is conceivable that in this study the COHb content was merely serving as an indicator for some more toxic component of cigarette smoke.

We may conclude that there is some evidence that severe CO exposure increases the risk of developing overt ischaemic heart disease, in man and in animals (Goldsmith and Aronow, 1975). However, the threshold concentration seems higher than that normally encountered in the urban environment (unless the individual is sensitized by simultaneous exposure to high altitudes). Furthermore, the vulnerable population is probably smaller than the 12% with atherosclerotic heart disease, being restricted largely to those with unstable angina and/or acute myocardial infarction.

14.1.3 Effects on Diseased Hearts

Ayres, Gannelli and Armstrong (1965) and Ayres et al., (1968, 1969) studied coronary gas pressures during bolus exposure to CO (100 Pa for 8-15 min, or 5000 Pa for 30-45 sec, COHb levels 6-12%). The coronary arteriovenous oxygen difference was widened, both in patients with normal vasculature and in those with coronary atherosclerosis, and there was an associated reduction of lactate extraction by the heart. Critics suggested the effect might arise from a poisoning of myocardial enzymes by the high CO transient, and in partial support of this suggestion, reactions were less at the lower CO pressure, despite an equal increase of COHb (Ayres et al., 1970). As in animal experiments (Adams, Erickson and Stone, 1973; Young and Stone, 1976) normal subjects were able to produce a partial compensation for CO poisoning by an increase of cardiac output and coronary perfusion (Adams et al., 1973; Ayres et al., 1968; 1969; Horvath, 1973) whereas neither cardiac output nor coronary flow were increased in those with coronary disease (Hersch, 1964). Permutt and Farhi (1969) estimated that a 20% increase of coronary blood flow would be needed to compensate for a 5% increase of COHb saturation in dogs. Adams et al., (1973) actually observed a 13% increase in coronary blood flow for 4% COHb, and a 54% increase for 20% COHb. Surprisingly, some reduction of arterial oxygen tension was seen during CO exposure. Possible explanations include an increased effect of venous-arterial shunting and ventilation-perfusion imbalance in the lungs, associated with the falling mixed venous oxygen content (Brody and Coburn, 1969), and a more direct effect of the altered shape of the oxygen dissociation curve. The myocardium of the anginal patients develops a typical "hypoxic" response during CO administration; Aronow et al., (1974) found an increase of end-diastolic pressures, with a decrease of left ventricular $\frac{dp}{dt}$, stroke index and cardiac output in response to 2.05% increase of carboxyhaemoglobin content.

Aronow and Rokaw (1971) showed that the smoking of lettuce-leaf (nicotine-free) cigarettes shortened the time to exercise-induced angina pectoris. The COHb level increased

from 1 to 8%, but other factors related to smoking may have contributed to the worsening of angina. The same criticism applied to early freeway exposures (Aronow et al., 1972). Exposures to CO were not double-blind (Theodore, 1973), and effects could have arisen from pollutants other than CO. On one day, experimental subjects were driven along the Los Angeles freeway in a vehicle with open windows; the ambient CO averaged 5.3 Pa, and over 90-min. exposure, blood COHb levels increased by the surprisingly large amount of 3.96% (to an average of 5.08%, Aronow et al., 1972; Haagen-Smit, 1966; Theodore, 1973). On this occasion, the endurance of a standard bicycle ergometer test diminished from 249 to 174 seconds. Ischemic ST depression also occurred earlier, after less exercise, and at a lower systolic blood pressure-heart rate product. On a second occasion, the drive was repeated while breathing compressed air; the COHb level dropped to 0.65%, and performance was unchanged relative to the initial control reading.

The experiment was later repeated in double-blind fashion in the laboratory, the subjects breathing in random order compressed air and compressed air containing CO. On the days that CO was breathed, COHb% increased by an average of only 1.65% (total 2.5-3.0%), while endurance time on the bicycle ergometer decreased from 224 to 188 sec. The systolic pressure/heart rate product at the onset of angina also diminished (Aronow and Isbell, 1973), although no ECG changes were seen in any of the exercise tests. "Passive smoking" aggravated angina at an even lower reading (COHb 1.8-2.3%), although here the situation may have been complicated by other components of the cigarette smoke (Aronow, 1978). Double-blind inhalation of CO was also tested on patients with intermittent claudication (Aronow, Stemmer and Isbell, 1974); this showed a reduction of exercise time from 174 to 144 sec in response to a 1.69% increase of COHb (total 2.8%).

Anderson et al., (1973) had subjects with stable angina breathe air or CO (5 or 10 Pa) for 4 hours prior to a treadmill walk. The time to angina was reduced equally in the two experimental conditions (Δ COHb 2.9 and 4.5%, respectively), although the larger dose of CO was associated with longer lasting pain. Five of the 10 subjects also had deeper ST-segment depression after CO exposure, although the change was not statistically significant. Surprisingly, neither dose of CO shortened the total possible duration of exercise.

K.H. Jones and J. Kuelson (In press, 1979) took data from the three experiments of the Aronow and Anderson laboratories, and attempted to fit a continuous function that would allow for differences in both initial time to angina, T, and initial COHb content. Their equation took the form:

$$\frac{\Delta T}{T_o} = f(\Delta \text{ COHb\%})$$

The data showed a very wide scatter, but at least in the case of Aronow's experiments a significant linear regression was demonstrated. Jones and Kuelson thus argued that there was no threshold for the worsening of angina - even a small increase of CO produced some adverse effect.

It has yet to be demonstrated that exposure to CO increased the frequency or the severity of chest pain; nor is it established that CO causes other complications or shortens life expectancy in the anginal patient (Coburn, 1979). Indeed, relatively few heart attacks occur during smoking (Kuller et al., 1975) or in other acute CO exposures. On the other hand, it is generally agreed that minor ECG abnormalities are exaggerated when middle-aged men (either the ostensibly healthy or those with overt ischaemic heart disease) have undertaken exercise after exposure to carbon monoxide (E.W. Anderson et al., 1971; 1973; Hackney et al., 1962). In animals, at least one study has shown that the electrical threshold for induction of ventricular fibrillation is less after prolonged carbon monoxide inhalation (10 Pa for 24 weeks, COHb around 9%, DeBias et al., 1976). Thomsen and Kjeldsen (1974) also described myofibrillar degeneration and myelin body formation in the mitochondria of rabbits exposed to 10 Pa for 4 hours, with a COHb level of 8 to 9%. Other authors, working with the monkey and the rat, have found no effect of 10 Pa CO over a 2-year period (Eckhardt et al., 1972; Stupfel and Bouley, 1970). Measures of cardiac function such as systolic time intervals remain unchanged with exposure to normally encountered CO levels.

14.2 Traffic Accidents

From the psychomotor changes discussed in previous sections, it might be anticipated that CO exposure would give rise to an increase of accidents in skilled tasks - particularly in vehicle driving, where high partial pressures of CO are encountered. However, little information is available on this point (Chovin, 1967; Clayton et al., 1960; Goldsmith, Beard and Dinman, 1969; Ury, Perkins and Goldsmith, 1972). Attempts to demonstrate a deterioration of vehicle-driving skills (Wright and Shephard 1978b; Wright et al., 1973) have shown relatively minor changes. Two possible explanations are (i) standard driving tasks fail to tax the "spare capacity" of the average driver (Brown and Poulton, 1961), so that this reserve can be exploited during CO poisoning, and (ii) a modest depression of cerebral function may optimize the "arousal" of the driver (Corcoran, 1965), thus maintaining or even improving performance. Epidemiological research relating accidents to ambient CO levels is hampered by the tremendous excess of alcohol-related

accidents and the difficulty in allowing for effects due to cigarette smoking; both the mechanics of smoking a cigarette and resulting heavy CO exposure could give rise to accidents, while smoking also has some correlation with alcoholism. Clayton et al., (1960) found 35% of drivers and pedestrians involved in accidents had a COHb level of greater than 3%, and Yabroff et al., (1974) also found an increased proportion of COHb readings greater than 5% among drivers involved in fatal accidents. A third study, from Los Angeles established a significant relationship between the frequency of accidents and the level of oxidant pollution, but found no relationship between accidents and CO exposure (Ury et al., 1972).

In some aircraft accidents, CO poisoning has been implicated, this being due to faulty oxygen equipment, cabin contamination by exhaust fumes, smoking, and fires (Blackmore, 1974; Howlett and Shephard, 1973).

15. AIR QUALITY CRITERIA AND OBJECTIVES

The choice of air quality objectives depends not only on scientific facts and their interpretation, but also on the values of a society - how much is the community prepared to sacrifice in terms of its standard of material well-being for clean air or indeed the health of a minority of the population (Biersteker, 1972). In the case of carbon monoxide, the argument assumes new poignancy with diminishing reserves of fossil fuel and the supposed conflict between clean and efficient use of the automobile engine (Heuss et al., 1971). Should one seek complete safety or merely "reasonable protection of public health" (Shy, 1973)?

Various models of the inter-relationship between air pollution and human health have been developed to emphasize the consequences of adopting a particular air quality standard (D.O. Anderson, 1967; Colucci et al., 1973; Goldsmith 1962; Goldstein, 1975; Hatch 1962; Phair and Sterling, 1969). Since carbon monoxide is colourless and odourless, aesthetic considerations are not a major concern. Some effects upon bacteria and leaf formation have been described at high doses, but the limiting factor is the influence of CO upon man.

Immediate practical issues are the possible existence of a "threshold", below which no response occurs, and the linearity of response at higher doses of CO. Some authors - for example Horvath and his associates have maintained that there is no change in maximum oxygen intake below a COHb saturation of 4%, although deterioration of response is a linear function of COHb levels above 6% saturation. Under resting conditions, reflex compensation (for example, a widening of arterio-venous oxygen difference) could maintain normal function, but this seems inherently less probable in maximum effort. If there is no threshold, then any accumulation of pollutant becomes undesirable; one must establish an acceptable level of risk, possibly by setting a monetary value upon human health or life (Duck, 1973; Goldberg, 1972). If indeed there is a threshold, this probably differs according to the physiological function being examined, and it becomes necessary to decide which functions are of significance to health (Ferris, 1978). The most vulnerable areas seem to be the heart, the brain, and exercising muscle.

Comparative analysis of the several human response models available reveals five possible levels of disturbance. The threshold for level A probably depends on test sensitivity; the exposure lies within the potential range for homeostatic adjustments, so that any response is transient and easily overlooked. The Russians (e.g. Glass, 1975; Ryazanov, 1962) have suggested that a pollutant must have no direct or indirect harmful or unpleasant effect upon man. It must not impair his working capacity, his mood, or his physical

well-being. Any need for "adaptation" is regarded as a deleterious reaction, and correspondingly stringent air quality standards are stipulated. The degree of enforcement of the regulations is unknown.*

In our free enterprise society (where cars, including the Lada, are more plentiful!), the extent to which an individual's physiological reserve can be exploited to achieve economic benefits remains a major issue (Stern, 1965). At level B, there are definite, persistent physiological effects, but the observed disturbances may have no significance for health (Heuss et al., 1971). At level C (warning level) there is some evidence of strain; the body's efforts at compensation are noticeable, and although exposures remain tolerable, they are becoming unpleasant. Levels D and E represent an emergency situation, with a risk of pathological changes and death respectively; hospital admissions increase, and the exposed population shows an excess mortality (Biersteker, 1976).

Levels of health and human responsiveness are distributed asymmetrically about a median line (Goldsmith, 1962). Thus even low level exposures to a particular pollutant can have an impact on the health status of a few sensitive members of a population. Goldsmith (1962) argued that community standards should reflect an "earliest effect" level for sensitive subjects rather than a "no effect" level for healthy persons; however, somewhat greater exposures might be acceptable in industry. Hatch (1973) suggested that industrial air quality standards should be set below the limit of physiological compensation, thereby allowing a reserve for (1) any unintentionally greater exposures and (2) impairment by age, residual illness, other environmental stresses and possible cumulative effects. Beard and Wertheim (1967) argued that the capability to perform a given task is also a valid criterion.

The ratio of occupational to ambient standards is another hotly debated philosophical issue. For NO_2, a ratio of 30:1 has been proposed by several authors (Morrow, 1975; Guidotti, 1978). Applied to CO, this would imply an 8 h average of only 0.17 Pa, with peaks of 0.67 Pa; such figures would be almost impossible to attain in a city, and indeed would leave little margin over "natural" levels. A more realistic approach for carbon monoxide is to decide upon an unsatisfactory COHb level (on physiological or pathological grounds), to estimate the ambient pattern of exposure needed to reach this limiting value, and then to apply some safety factor to allow for individual differences in exposure and sensitivity. Unfortunately, commonly accepted safety margins again seem

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* The casual impression of the visitor is that vehicle densities are low, but that there is much industrial pollution from low, poorly-designed and poorly-sited chimneys.

impracticable for CO. Morrow (1975) has argued that there is a parallel between contamination of foodstuffs and the intake of a pollutant that is continuous but highly variable. According to the U.S. Food and Drug Administration, there should be a 100-fold margin between the dose not producing an effect in two species of animals (A CP pressure of ~ 2.5 Pa) and that considered safe (an unrealistic 0.025 Pa). While a 100-fold margin may be desirable to protect the population from death, carcinogenesis and teratogenesis, it is probably too large for such phenomena as impaired time judgment.

Canada currently specifies both acceptable and desirable objectives for ambient air (Ouellet, 1978), but this has a potential for confusion, and a single standard might be preferable. Two prime criteria for unsatisfactory blood COHb levels emerge from this review. The lowest figure is that which hastens the onset of exercise-induced angina. In nonsmoking patients sensitized by coronary atherosclerosis, this occurs when the blood COHb level increases from its baseline to 2.5-3.0% saturation. Based on the assumption that individuals with pre-existing cardiovascular insufficiencies are screened from specific occupations, the second criterion is the performance deterioration related to changes in the functioning of the central nervous system. This is realized when the blood COHb level of the nonsmoker increases to 3 to 4% saturation. The corresponding ambient levels can be deduced from Tables 2 and 4.

Currently proposed standards (Table 1) have been based on these general considerations, with varying safety margins. For example, the U.S. time weighted 8-hour average of 8.6 ppm (~ 0.86 Pa) has been designed to keep the COHb level below 1.5 to 2%. This may be a difficult goal to realize. For example, the blood donor studies of Stewart et al., (1974) found 25 to 75% of supposed nonsmokers with excessive levels of COHb in various large U.S. cities. Nevertheless, critics have pressed for more exacting standards, arguing that insufficient allowance is made for (i) the speeding of CO absorption by physical activity (Table 3), and (ii) transient peaks of CO. The first criticism is warranted, since the subjects of the key experiment were sitting in a car throughout exposure. The second criticism is less valid, since peaks of pollution were probably encountered during the car journey.

Other limitations of the standard include a need for more data on (i) various high risk groups (the foetus and newborn, the aged and patients with anaemia, surgical shock, chronic respiratory disease, and cerebrovascular disease), and (ii) possible interaction with other stressors such as high altitude (a ppm standard in itself increases exposure levels at altitude).

The U.S. standards can only be exceeded once per year, which means that the regulations relate to extremely rare weather conditions. The Canadian use of an average concentration or some more complete description of the data has some advantages. The 8 h and 1 h averages must provide the main basis of control in view of the body's capacity to equate brief exposure to very high concentrations and sustained low-level exposure. However, to the extent that there is some difference of CO distribution between a bolus and a steady-state exposure, there may be grounds for at least spot-checks of peak ambient levels averaged over 5-min or less.

Table 1 - World recommendations for Air Quality

	WHO secretariat (WHO, 1979)	Canada (Ouellet, 1978)		U.S.A. (Environmental Protection Agency, 1971)				Japan (Environment Agency 1975)	West Germany (Federal Minister of Interior, 1974)	Russia (Krotov, 1975)
Time Period		Acceptable	Desirable	Max. permissible level	Warning	Emergency	Health Hazard			
15-min or less	100 ppm ceiling (10 Pa)									
30-min	50 ppm TWA* (5 Pa)									
One-hour	25 ppm TWA* (2.5 Pa)	30 ppm A† (3.0 Pa)	13 ppm A† (1.3 Pa)	35 ppm M†† (3.5 Pa)			125 ppm (12.5 Pa)			
8 hours	13 ppm TWA* (1.3 Pa)	13 ppm A† (1.3 Pa)	5 ppm A† (0.5 Pa)	8.7 ppm M†† (0.87 Pa)	30 ppm (3.0 Pa)	40 ppm (4.0 Pa)	50 ppm (5.0 Pa)	20 ppm A† (2.0 Pa)	26 ppm** (2.6 Pa)	
24 hours	10 ppm TWA* (1.0 Pa)							10 ppm A† (1.0 Pa)	9 ppm A† (0.9 Pa)	0.9 ppm (0.09 Pa)
Permitted COHb for nonsmokers×	2.5 - 3.0%			1.3% - 2.9%						

ppm = parts per million

* Time-weighted average

† Average concentration

†† Maximum not to be exceeded > once per year

** 95% value of cumulative frequency distribution

× Equivalent predicted COHb varies with equation used and activity level of subjects.

Table 2 - Difference in predicted COHb% during exposure to CO pressure of 10 Pa using models of several authors

Rest			Light Exercise			Author
15-min	60-min	480-min	15-min	60-min	480-min	
1.0	2.3	14.4	1.7	5.3	38.4	Forbes et al., (1945)
0.8	1.9	11.5	1.6	4.7	34.1	Pace et al., (1946)
1.1	2.8	10.9	1.9	5.4	14.6	Hanks and Farquhar (1969)
1.5	3.5	13.0	-	-	-	Peterson and Stewart (1970)
1.2	3.0	12.4	2.0	5.7	15.9	Coburn et al., (1965)

Table 3 - Influence of physical activity upon COHb% (Data based on model of Coburn et al., 1965). S = sedentary, M = moderate activity, H = heavy work* (from WHO, 1979)

CO pressure	15-min			60-min			8-hour		
	S	M	H	S	M	H	S	M	H
20 Pa	1.8	3.5	5.2	5.4	11.0	15.5	24.5	31.7	32.9
5	0.82	1.2	1.6	1.7	3.0	4.1	6.4	8.0	8.3
2.5	0.66	0.84	1.0	1.1	1.7	2.2	3.3	4.1	4.2
1	0.55	0.61	0.67	0.71	0.90	1.1	1.5	1.7	1.7
0.5	0.52	0.54	0.56	0.58	0.63	0.68	0.91	0.91	0.89

* Sufficient to induce a diffusing capacity of 60 mL/min/mm Hg, and a ventilation of 30 L/min.

Table 4 - Anticipated COHb levels of a healthy resting nonsmoker exposed to known CO concentrations for specified period. Values are estimated from the data of Forbes et al., (1947) and Peterson and Stewart (1970)

Partial pressure of respired CO	COHb% and Duration of Exposure						
	10-min.	15-min.	30-min.	1-hour	3 hours	8 hours	Equilibrium
Endogenous CO	0.4	0.4	0.4	0.4	0.4	0.4	0.4
0.5 Pa				0.5	0.6	0.8	0.9
1 Pa			0.5	0.6	1.1	1.7	1.8
1.5 Pa			0.6	0.7	1.4	2.4	2.7
2 Pa		0.5	0.7	0.9	1.7	3.0	3.5
3 Pa	0.5	0.6	0.8	1.3	2.4	4.5	5.0
4 Pa	0.6	0.7	1.0	1.5	2.8	5.9	6.1
5 Pa	0.7	0.8	1.3	1.9	3.5	7.0	7.8
7.5 Pa	0.8	1.2	1.7	2.6	5.0	9.6	11.0
10 Pa	1.1	1.4	2.2	3.0	6.5	12.5	14.0
20 Pa	1.9	2.5	4.0	6.0	12.5	20.0	24.6

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